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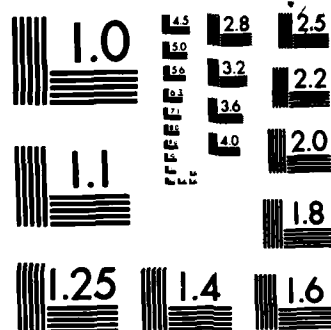NATIONAL BUREAU OF STANDARDS 1963-A

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BLOOD TRANSFUSION THERAPY IN PATIENTS WITH HEART DISEASE

by

C. R. VALERI

NAVAL BLOOD RESEARCH LABORATORY
BOSTON UNIVERSITY SCHOOL OF MEDICINE
615 ALBANY ST.
BOSTON, MA 02118

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The oxygen transport function of preserved red cells transfused to anemic patients who have heart disease is critical. Patients with heart disease should be given red cells with normal 2,3 DPG and normal affinity for oxygen instead of low 2,3 DPG red cells. Our studies suggest that red cells with high 2,3 DPG (150 to 200% of normal) and low affinity for oxygen are the best form of transfusion therapy for anemic patients, especially those with congestive heart failure. It may even prove useful to use 2,3 DPG-enriched red cells in patients with patchy myocardial ischemia and

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at any rate, it can do no harm. High 2,3 DPG red blood cells also are recommended in patients with right-to-left cardiac shunts and pulmonary shunts, provided that the inspired ambient oxygen tension is adequate to maintain an arterial pO_2 tension of greater than 40 mm Hg.

Blood products utilized during extracorporeal bypass surgery should ensure optimum oxygen delivery to tissue and maintain or restore normal hemostasis, and red cells with 250% to 300% of normal 2,3 DPG and low affinity for oxygen given in combination with crystalloid solution will do this. Red cells with elevated 2,3 DPG levels do ensure optimum delivery of oxygen to tissue, especially during hypothermia, although it cannot be stated definitely whether or not they reduce myocardial damage.

A postoperative bleeding diathesis following cardiopulmonary bypass due to a decrease in platelet number and to abnormalities of platelet function should be treated with platelet transfusions. Although a bleeding diathesis as a result of dilutional coagulopathies is rare, severe dilutional coagulopathies should be treated with fresh frozen plasma. However, routine use of fresh frozen plasma following cardiopulmonary bypass is not recommended.

Introduction

Of the various complications that might affect the clinical course of patients suffering from various types of heart disease, anemia is one of the most serious. This is because the most prominent manifestations of anemia involve cardiorespiratory function. Thus, the relation between the two must be understood to adequately treat these patients.

When the cardiac patient requires surgery, especially an operation involving the heart itself, almost always with the use of heart-lung devices, an enormous stress is placed on the heart even though global cardiac function may be normal or almost so. We will discuss in this chapter the indications for red cell transfusions in anemic patients with heart disease both in the presence and absence of congestive failure. In particular, we will discuss the effects of the quality of the transfused red blood cells in the treatment of the cardiac patient, and the indications for specific blood products, i.e., the use of red blood cells, platelets, and plasma, in treating patients during extracorporeal bypass at normothermic and hypothermic temperatures.

Indications for blood transfusions and recipient's state of health

The recipient's state of health determines which blood products are indicated. Patients who are undergoing cardiopulmonary bypass surgery for coronary artery disease but are in otherwise good health will not require the same transfusion therapy as patients with valvular heart disease who have congestive heart failure and hepatosplenomegaly. In these latter patients, the severity of the heart disease, and the presence of pulmonary congestion, hepatosplenomegaly, bone marrow abnormalities, or renal disease, must be considered in the use of transfusion therapy.

In the anemic patient with heart disease, assessment of blood volume is of primary importance. Chronic congestive heart failure is known to cause increases in blood volume in general,[1] but the determination must be made at the time that the patient presents with anemia whether he has hypovolemia, normovolemia or hypervolemia associated with the red cell volume deficit. An accurate assessment of a deficit in red cell volume cannot always be made from the patient's hematocrit value. Plasma volume usually is increased in congestive heart failure. More-over, certain drugs may reduce plasma volume and raise the hematocrit level, and splenomegaly will further reduce the peripheral venous hematocrit value. An increase in plasma volume may be secondary to retention of salt and water by the kidneys.

The clinical assessment that transfusion therapy is necessary is based on the finding of a reduced hematocrit or hemoglobin level in the

peripheral venous blood. The peripheral venous hematocrit reflects the red cell volume, the plasma volume, and the size of the spleen.[2-8] In the presence of splenomegaly, there is an increase in plasma volume and a reduction in red cell volume due to sequestration of red cells in the spleen. Transfusion therapy should not be initiated merely to correct a low hematocrit level or hemoglobin concentration; rather, an evaluation should first be made of the patient's clinical status and laboratory data. Hypovolemia in general can be diagnosed clinically by postural changes in blood pressure and pulse rate.

Chronic Anemia

Chronic anemia may develop 1) after a large hemorrhage without adequate blood replacement, 2) after repeated undetected small losses of blood, perhaps accompanied by nutritional iron deficiency, 3) as a result of bone marrow depression, or 4) any combination of these.

Compensatory mechanisms in anemia

The cardiorespiratory compensations in chronic anemia are well known and include increased respiratory volume, increased cardiac output, decreased oxygen affinity of red cells, and changes in blood volume. The first detected change is an increase in respiratory minute

volume out of proportion to the body's metabolic requirements, which results in an increase in the alveolar air oxygen tension available for saturating the hemoglobin in the pulmonary capillaries, and compensates to some extent for the fall in blood oxygen-combining power induced by anemia. This causes a slight degree of respiratory alkalosis, and may result in a reduction in cerebral blood flow although the increase in cardiac output that occurs in anemia usually compensates for this reduction.

The cardiac output begins to increase when the blood hemoglobin concentration falls to between 8 and 10 grams per 100 ml (Fig 1).[9-12]   FIG 1 At hemoglobin levels of 5 gm/dl, the increase in cardiac output is substantial. Since the body's total oxygen consumption remains normal or close to it, the systemic arterio-venous oxygen difference is smaller than expected. The mechanism that underlies the rise in cardiac output is not completely understood, although widespread vasodilation occurs as shown by a marked decrease in total peripheral resistance. The vasodilation is not the same throughout the body and indeed may be absent in skin and kidneys.

A third compensatory mechanism that increases the oxygen delivery to tissues is a change in the oxygen dissociation curve.[12,13] Red blood cells with a low affinity for oxygen produce an accelerated unloading of oxygen to the tissues. This change in the curve results from an increase in red blood cell 2,3 DPG, owing to a change in erythrocyte carbohydrate metabolism.[14-18]

Yet another compensatory mechanism in chronic anemia is an increase

in plasma volume such that the total blood volume may be normal or even increased despite a low red blood cell mass. The increased plasma volume may be due to retention of salt by anemic patients,[19] but the phenomenon as a whole is not understood. At any rate, the increase in blood volume found in chronic anemia prevents the development of oligemic anemia such as occurs in trauma,[20] a disorder in which the plasma volume remains so low that the hematocrit percentage is normal despite the decreased red blood cell mass.

Aggravation of symptoms by anemia in cardiac patients

Anemia is known to aggravate cardiac disorders in a variety of ways. Anemia induces an increase in cardiac work, and attacks of angina pectoris due to coronary atherosclerosis are made worse and more frequent by the development of anemia. The occurrence of pain may be due to an increase in cardiac muscle work without a corresponding increase in coronary blood flow in regions with rigid, narrowed arteries or with inadequate circulation due to blockage. (This is to be distinguished from the myocardial infarction that may occur when massive hemorrhage produces shock.)

In chronic congestive heart failure there is myocardial insufficiency. The heart muscle is inefficient, with a low ratio of work done-to-energy consumed. Digitalis, which increases muscle work in the failing heart, also increases cardiac muscle efficiency. Anemia, pregnancy, fever, hyperthyroidism, and drugs such as epinephrine and aminophylline, as well as some other factors, increase the work of the cardiac muscle without increasing its efficiency. This in time will aggravate myocardial

insufficiency. Whether the symptoms of cardiac failure are due to cardiac strain or produced by excessive salt retention, the symptoms improve when the anemia is cured.

Treatment of chronic anemia in cardiac patients

There may be differences in the mode of treatment among various patients with heart disease aggravated by chronic anemia. In some cases it might be appropriate simply to stop any bleeding and to treat the anemia medicinally. However, in most cases blood transfusions are required, and then the question is the quantity and kind of blood products. Since all blood products must be given by vein, the effects of large intravenous infusions also must be considered.

The "overloaded" circulation

Over a century ago in Germany, a common diagnosis in man was "beer-drinkers heart", the theory being that these individuals had drunk so much beer as to have "overloaded their circulation", and the "overloaded circulation" caused massive cardiac hypertrophy and ultimately death.

When the work of the heart was finally calculated, it was found to be:

$$W = O \times \text{Mean BP} + \frac{wv^2}{2\,g}$$

where W is work, O is output of a ventricle, mean BP is self-evident, w is the weight of blood, V is the velocity of blood in the aorta, and g is the gravitational constant. Thus, the volume of circulating blood is not a factor. The effects of an intravenous infusion on cardiac work are negligible. When the cardiac output is 4.0 liters per minute, an intravenous infusion at a rate of 20 ml per minute will increase it to 4.020 liters, a change so insignificant as to be noteworthy only to academicians.

When intravenous infusions are given, sodium chloride may accumulate locally, particularly in collagen, which makes up 60% of the lung. Cohnheim and Lichtheim[21] in 1877 studied the development of pulmonary edema in rabbits given isotonic saline solution intravenously, and found that pulmonary edema developed only after the animals received half their body weight of solution within 30 minutes, obviously a far greater dose than patients would receive. To produce pulmonary edema in dogs in this way, the amount of solution equal to the body weight of the animal must be infused within 30 minutes. The physiology of man being different from that of rodents and canines, in normal persons an intravenous infusion of 1500 ml of isotonic saline solution given within a 10- to 30-minute period causes no detectable changes in the lungs.[22] In patients with moderate or severe congestive heart failure, a dose of 1500 ml within 30 minutes may cause a decrease in vital capacity and the appearance of a few rales.[22] There is no reason to expect that blood transfusions in the usual volume would have any adverse effects

on cardiopulmonary function because of "overload".

Although this theory would appear to be refuted by the substantial accumulation of data from intensive care units devoted to the resuscitation of patients with severe trauma, many of the patients studied were given human serum albumin solution, which is known to decrease cardiac inotropic function[23] and to increase pulmonary capillary permeability. Much of the infused material never reached the left ventricle, making conclusions based on relations between pulmonary artery pressures and left ventricle work invalid. Moreover, when whole blood was used, no mention was made of the fact that stored plasma also increases pulmonary capillary permeability,[24] nor was the quality of the transfused red blood cells defined, even though it is known that cells with low 2,3 DPG levels may adversely affect cardiac function.[25,26] Further, studies have shown that some patients who do not receive intravenous fluids during operations have exactly the same pulmonary vascular changes as those who do receive infusions.[27] In reality, there is nothing in clinical or experimental medicine to substantiate the concept of "overload".

Discounting "overload" as an objection to transfusion therapy in cardiac patients, other factors should be considered. The first pertains to the liquid component of the blood, and the second pertains to the quality of the red blood cells. As regards the first, mention has already been made of the finding that serum albumin solution and week-old plasma

increase pulmonary capillary permeability.[24,28,29] In view of the
tendency toward pulmonary edema in heart disease, it is important to
avoid anything that might exacerbate this tendency, including plasma
and albumin solution. The observation that stored whole blood depresses
the metabolism of skeletal muscle suggests that a similar depression
might also occur in cardiac muscle,[30,31] although there are no conclusive
data on this.

In addition to the accumulation of inimical substances in the
plasma of blood during liquid storage, some erythrocyte changes that
occur during storage may produce adverse effects. After approximately
5 days of storage in CPD anticoagulant, the red blood cell 2,3 DPG level
falls markedly,[25,32-34] and the hemoglobin oxygen dissociation curve is
so changed as to impair the unloading of oxygen in the tissues. Published
studies have shown the adverse effects of perfusing various tissues with
red blood cells that have low 2,3 DPG levels, whether as a direct result
of a lack of oxygen or due to some other metabolic change, and present
evidence to show that low 2,3 DPG blood should not be given to cardiac
patients.[25] What the anemic cardiac patient needs is washed plasma-free
red blood cells suspended in as little salt solution as possible, and
with 2,3 DPG levels that are normal or increased.

Patients with congestive heart failure accompanied by chronic anemia
usually suffer "high output" failure and relative renal insufficiency.
Whether or not the patient has congestive heart failure, a hemoglobin
concentration of 10 g% or less should be treated with red blood cells to
provide oxygen carrying and oxygen delivery capabilities. The transfused

red cells should have posttransfusion survival values of at least 70%, and red cell oxygen transport should be normal or improved to ensure optimum oxygen delivery to the tissues, especially to the myocardium. Once the anemia is treated and the delivery of oxygen to the heart is improved, it is possible that myocardial function may be improved or restored to normal.

The volume and composition of the fluid administered to patients in chronic congestive failure may influence the symptoms of underlying cardiopulmonary insufficiency. Acute phlebotomy followed by the infusion of red cell concentrates might be effective in the treatment of acute hypervolemia in anemic patients with chronic congestive heart failure.

Treatment of anemic patients with heart disease

Red cell concentrates are the treatment of choice for anemic patients with chronic congestive heart failure. Usually a volume of 100 to 150 ml of sodium chloride solution is used to dilute the red blood cell concentrates to ensure adequate flow.[35] When unwashed red blood cell concentrates that still contain some plasma are transfused, a smaller volume of sodium chloride is recommended. When the unwashed red blood cell concentrate has a hematocrit value of 80 V%, a volume of 10 to 15 ml of isotonic saline may be used to dilute the red cell concentrate for adequate flow through an ultrapore filter. The flow of washed liquid-stored or previously frozen red blood cell concentrates is satisfactory when the hematocrit value is greater than 90 V% at the

time of transfusion.[36] Ultrapore filters (40 micron or less) are recommended for the administration of blood products to patients with heart and lung disease in order to remove as much of the micro-aggregate material as possible.[25,37,38] Patients with chronic congestive heart failure subjected to acute hemorrhage or operative shock may be treated with crystalloid and colloid solutions together with red blood cell concentrates.[39-45] Because of the increased pulmonary capillary permeability in patients with chronic congestive failure, 25 to 50 grams of salt-poor albumin and 5% albumin solution may be advisable. Although it is true that albumin solutions remove the problem of posttransfusion hepatitis, one cannot ignore the potential adverse effects of albumin on myocardial function,[23] pulmonary function,[28,29] clotting system,[46-48] renal function,[49,50] and the immunologic state[51] of the recipient.

Acute hypovolemic shock in a patient with congestive heart failure can be treated with fresh frozen plasma, but there are potential hazards associated with such treatment, i.e., the risk of allergic reactions[52] and posttransfusion hepatitis.[53-56] Acute hemorrhagic shock in patients with chronic congestive heart failure should not be treated with large volumes of isotonic crystalloid solution and hypertonic sodium chloride, because the salt in these solutions is retained by the patient, producing excessive edema especially in the lungs. Red blood cells produce an increase in red cell volume followed by a prompt and satisfactory increase in plasma.[20] They do not themselves have an oncotic effect in vitro, but they do produce an in vivo increase in plasma volume, apparently by

the mobilization of interstitial albumin when closed capillaries are re-opened and perfused.

How does one determine if red blood cells have normal oxygen transport function? For normal individuals with normal adult hemoglobin, the red cell oxygen transport function is determined from temperature and from red cell 2,3 DPG, ATP, pH, and pCO_2 levels.[25,34,57] These factors affect the red cell affinity for oxygen which is usually reported as the partial pressure of oxygen (mm Hg) needed to saturate 50% of the hemoglobin at pH 7.4 and a pCO_2 of 40 mm Hg. An increase in red cell 2,3 DPG usually is seen in patients with anemic hypoxia, hypoxic hypoxia, or stagnant hypoxia.[13,25,57] Red blood cells with increased 2,3 DPG have a decreased affinity for oxygen, and this facilitates the unloading of oxygen in the tissues.

Red cell 2,3 DPG is usually increased as a pathophysiological adaptation to anemic hypoxia, hypoxic hypoxia, or stagnant hypoxia.[12,57] The increase in red cell 2,3 DPG that occurs during anemic hypoxia allows for a decrease in red cell volume by about one-third before cardiac output increases to compensate for the decrease in the number of red cells (Fig 1). In a normovolemic anemic individual, cardiac output increases in response to a reduction in hemoglobin concentration to less than 10 g%. An increase in red cell 2,3 DPG from 0.9 moles DPG per mole of hemoglobin (13 uM/g Hb) to 1.5 moles of DPG per mole of hemoglobin (22 uM/g Hb) usually is observed in normothermic patients with anemic hypoxia.[12,57] Cardiac output does not increase until the red cell volume is decreased by greater than one-third and until the

2,3 DPG has risen to 1-1/2 to 2 times normal and the red cells have improved their oxygen delivery capacity (Fig 1).

Patients with coronary artery disease with or without cardiomegaly usually have normal red cell volume and normal red cell oxygen transport function.[1,13] When the patient has valvular heart disease or myocardiopathy with cardiomegaly, he may have normal or increased red cell and plasma volumes and red cells with normal or only slightly elevated 2,3 DPG levels.[20] Patients with heart disease and congestive heart failure usually have red cells with 150% of normal 2,3 DPG levels and improved oxygen transport function.[13,25,57] Cyanotic heart disease with right-to-left shunts produces arterial hypoxemia, and these patients usually have red cells with 150 to 200% of normal 2,3 DPG levels.[58,59] The oxygen transport function of the preserved red cells transfused to patients with heart disease with or without congestive heart failure should be similar to that of the recipient's own red blood cells.[60]

To ensure acceptable posttransfusion survival values and normal or slightly increased 2,3 DPG levels, the red cell concentrates should be prepared from the unit of whole blood within 6 to 8 hours of collection. When the hematocrit value of the red cell concentrate is 80 V%, the unit can be stored at 4 ⌐ for 3 to 5 days with near normal 2,3 DPG levels. As a matter of f   ing storage of blood in CPD or CPDA-1 for 24 to 48 hours at 4   ; an increase in the red cell 2,3 DPG level (Figs 2-5).[61-63] The increase in red cell 2,3 DPG occurring in red cell   FIGS 2-5 concentrates during the 24- to 48-hour period of 4 C storage represents a form of "cold rejuvenation". During the first 10 days of storage at

4 C, red cell 2,3 DPG is maintained better in stored red cell concentrates than in stored whole blood (Figs 2-4).

The anticoagulant in which the red cell concentrate or whole blood is stored affects the maintenance of red cell 2,3 DPG. The citrate in the anticoagulant causes the red cell pH to rise, and this increase is intensified as the red cells are stored in the anticoagulant at 4 C.[63] Glycolysis is stimulated by an increase in pH, and glycolysis in the presence of phosphate in the anticoagulant causes synthesis of 2,3 DPG during the first 24 to 48 hours of 4 C storage. Thereafter, the 2,3 DPG level begins to fall, and after 2 weeks of storage in CPD or CPDA-1 is reduced to about 10% of normal.[25] Red cells with 10% of normal 2,3 DPG levels, increased oxygen affinity and low P50 values have been shown to adversely affect cerebral and myocardial function under certain circumstances.[25] When the 2,3 DPG level is 70% of normal or less, the red cells have an increased affinity for oxygen.

Preservation of red cells with normal or low affinity for oxygen

The red cell 2,3 DPG level and thus oxygen transport function is better maintained during the first 3 to 5 days of 4 C storage when CPD or CPDA-1 is used as the anticoagulant and when the unit is stored as a red cell concentrate rather than as whole blood. After liquid storage at 4 C for 3 to 5 days in CPD or CPDA-1 anticoagulant,[34] red blood cells can be frozen to ensure maintenance of 2,3 DPG (non-rejuvenated). Alternatively, a biochemical modification process can be employed to increase or restore the 2,3 DPG levels of indated and outdated red blood

cells after storage at 4 C in CPD or CPDA-1 (rejuvenated).[25,63-68]
Rejuvenated red cells must be washed before transfusion whether or not
they are subsequently frozen to remove the rejuvenation solution.[63]
Red cells frozen with 40% W/V glycerol at -80 C or with 20% W/V glycerol
at -150 C are washed before transfusion to remove the glycerol, whether
or not they have been rejuvenated.[69,70]

Rejuvenation of indated red blood cells increases 2,3 DPG levels
to 250% of normal, and biochemical treatment can increase the 2,3 DPG
level of outdated red cells to 150% of normal (Figs 6-8). Biochemically   FIGS 6-8
treated red blood cells have been stored in the frozen state for at
least 4 years, with satisfactory posttransfusion results.[63,67]

Rapid infusion of red blood cell concentrates in patients with cardio-
pulmonary insufficiency

A study was made to evaluate the safety of infusing red cells at
a rapid rate to elderly patients with cardiopulmonary insufficiency.[66]
Eleven such patients (mean age 70; range 66-83) each was administered
a pool of from 4 to 10 units of washed previously frozen red cells with
a hematocrit of 70 V% within 60 minutes through a 40 micron or 170 micron
blood filter. These red blood cells had been stored at 4 C for 22 to 28
days, biochemically treated to increase 2,3 DPG to 150% of normal and ATP
to 175% of normal and to improve oxygen transport function, and frozen
with 40% W/V glycerol at -80 C (Fig 9). After frozen storage at -80 C,   FIG 9
the red cells were thawed and washed and stored in the final wash solution
at 4 C for 24 hours. On the day of transfusion, the washed red cells

were concentrated by centrifugation to remove the supernatant solution. Four to 10 units were pooled and were transfused rapidly as a pool to these elderly patients. The rapid infusion of these red cells with improved oxygen transport function improved cardiopulmonary symptoms and produced no adverse effects, contrary to the apprehension that cardiopulmonary insufficiency might be aggravated.

Comparisons of red blood cells with low 2,3 DPG and high affinity for oxygen to red blood cells with normal 2,3 DPG and normal affinity for oxygen

A number of studies have been made to compare the therapeutic effectiveness of red cells having low 2,3 DPG and high affinity for oxygen (stored blood) with red cells having normal 2,3 DPG and normal affinity for oxygen (fresh blood).[25,71]

In a study by Collins and Stechenberg, rodents were exchanged with either stored blood (low 2,3 DPG) or fresh blood (normal 2,3 DPG).[72] After the exchange transfusion, the rodent's red cell volume was adjusted to either a normal or a decreased level and hemorrhagic shock was produced. The rodents with a decreased red cell volume and a hematocrit of 22 V% exhibited significantly increased mortality after the transfusion of stored blood (low red cell 2,3 DPG and high affinity for oxygen) than after transfusion of fresh blood (normal red cell 2,3 DPG and normal affinity for oxygen). This study in rodents which involved a combination of reduced red cell volume and red cells with low 2,3 DPG and increased affinity for oxygen represented a simulation of the clinical condition of

resuscitation of massively injured individuals with large volumes of stored blood, in which condition the patients usually are anemic and have in their circulation donor red cells with low 2,3 DPG and high affinity for oxygen.

Malmberg and his associates[73] also have exchange-transfused rodents prior to inducing hemorrhagic shock. Following exchange transfusions of red cells with low 2,3 DPG and high affinity for oxygen or red cells with normal 2,3 DPG and normal affinity for oxygen, the red cell volume was normal with a hematocrit value of 40 V%. Oxygen consumption and cardiac output were significantly lower and mortality was significantly greater in the rodents treated with red cells with low 2,3 DPG and high affinity for oxygen.

It is noteworthy that in both the Malmberg study[73] and the Collins and Stechenberg study,[72] higher mortality rates were seen when low 2,3 DPG red cells were used, even though in one study nonanemic rodents were exchange-transfused and in the other study anemic rodents were used, and there has been no explanation for these discrepancies.

Woodson and co-workers[74,75] found that rodents exchange-transfused with red cells with normal 2,3 DPG and normal affinity for oxygen showed only minimal changes in cerebral and coronary blood flow as long as their red cell volumes were normal. On the other hand, when red cells with low 2,3 DPG and high affinity for oxygen were used in the exchange transfusions and the red cell volumes were normal, cerebral and coronary blood flow was doubled. In some rodents with a red cell volume reduced to a hematocrit value of 22 V%, the exchange transfusion with red cells

with low 2,3 DPG and increased affinity for oxygen caused the cerebral blood flow to triple and the coronary blood flow to quadruple. The increases in coronary and cerebral blood flow could not be attributed either to an increase in cardiac work or to hypercapnia. The combination of anemia and red cells with low 2,3 DPG and high affinity for oxygen produced an increase in cerebral and coronary blood flow to compensate for a decreased tissue oxygen tension. Patients who are not able to compensate for a reduced red cell volume and impaired oxygen transport function by increasing cerebral and coronary blood flow, could suffer impairment of myocardial and cerebral function.

In a study by Holsinger and associates,[26] red blood cells depleted of 2,3 DPG were infused into the circumflex coronary artery of a dog with an anterior infarct that had been induced by occlusion of the left anterior descending artery. During the infusion of red cells with low 2,3 DPG and high oxygen affinity, the left ventricular end-diastolic pressure increased and ST segment elevation occurred. These investigators contend that even though this was a pilot study, it provided direct evidence that preserved red cells with low 2,3 DPG and high affinity for oxygen produce myocardial ischemia when coronary blood flow is kept constant.

When Woodson and co-workers[76,77] perfused red cells with low 2,3 DPG levels and increased oxygen affinity at a normal but fixed cerebral blood flow to an isolated dog brain, they observed decreased cerebral oxygen consumption, decreased jugular venous pO_2 tension, and abnormalities of the electroencephalogram. Subsequent perfusion with red cells with normal 2,3 DPG levels and normal affinity for oxygen resulted in

restoration to normal of cerebral oxygen consumption, jugular venous pO$_2$, and electroencephalogram.

These numerous studies in both rodents and dogs indicate that in the presence of normal vasomotor function of the coronary and cerebral blood, there usually are no adverse effects from red cells with low 2,3 DPG levels and increased affinity for oxygen. However, when there is impairment in vasomotor function of cerebral and coronary blood vessels, these red cells may produce an impairment in cerebral and myo-cardial function. From these findings, it is reasonable to assume that patients with heart disease should not be administered red blood cells with low 2,3 DPG levels and increased affinity for oxygen.

Comparisons of red blood cells with low 2,3 DPG and high affinity for oxygen and red blood cells with elevated 2,3 DPG and low affinity for oxygen

In a study by Rice and his associates[78] in which baboons in hemorr-hagic shock were resuscitated with red cells with either high or low 2,3 DPG levels, the red cells with 150% of normal 2,3 DPG restored oxygen consumption and hemodynamic measurements at lower cardiac output than did red cells with only 10% of normal 2,3 DPG.

Moores and associates[79] compared perfusions of pig red blood cells with low 2,3 DPG and high affinity for oxygen and pig red blood cells with slightly elevated 2,3 DPG and low affinity for oxygen, and found that when the hemoglobin concentration was 10 g%, the low 2,3 DPG red cells decreased the stroke volume significantly during extracorporeal

bypass at normothermic temperature.

Apstein and co-workers[80] studied the perfusion of isolated rabbit hearts with human red cells having 10% of normal 2,3 DPG or 150% of normal 2,3 DPG at normothermic and hypothermic temperatures. These investigators noted that at both 30 C and 37 C, the high 2,3 DPG red blood cells produced a greater improvement in oxygen consumption and myocardial function under basal conditions and after stimulation with isoproterenol. In this study, coronary blood flow was maintained at a constant rate to simulate conditions of fixed coronary blood flow.

Comparisons of red cells with normal to slightly reduced 2,3 DPG and normal affinity for oxygen and red cells with 120 to 150% of normal 2,3 DPG and low affinity for oxygen

Pantely and associates[81] used intravenous infusions of a solution containing pyruvate, phosphate and dihydroxyacetone, in dogs to increase the red cell 2,3 DPG levels to 120% of normal and improve oxygen delivery by increasing the P_{50} value by 2 to 3 mm Hg. Although these investigators observed no significant changes in the size of induced myocardial infarction, they did see changes in the volume of the vascular bed of the coronary circulation, and they offer the speculation that red cells with high 2,3 DPG and low affinity for oxygen may increase oxygen delivery to ischemic myocardium when flow is restricted.

Dennis and associates[82] studied patients coming off cardiopulmonary bypass, 11 of whom had been given 6 units of rejuvenated previously frozen washed red blood cells with 150% of normal 2,3 DPG, and 11 patients of

whom had received 6 units of nonrejuvenated liquid-stored nonwashed red blood cells with 70% of normal 2,3 DPG. Immediately following cardio-pulmonary bypass, the patients who received rejuvenated previously frozen washed red blood cells had P_{50} values of 31.6 mm Hg, whereas the patients who received nonrejuvenated liquid-stored nonwashed red blood cells had values of 28.3 mm Hg ($p < 0.05$) (Fig 10). Oxygen consumption values were 135 and 106 ml/minute/m^2 respectively ($p < 0.05$). Mixed venous oxygen tensions were similar in the two groups, but the arteriovenous content difference was higher in the group who received the rejuvenated red blood cells ($p < 0.05$). Fluid load produced a significantly greater increase in cardiac indices at comparable filling pressures in patients who received rejuvenated red blood cells than in the patients who received nonrejuvenated red blood cells (Fig 11). It has been suggested that the improved cardiac output may have been due to the fact that the rejuvenated red blood cells were washed before transfusion and washing removes citrate, whereas the nonwashed nonrejuvenated red cells contained citrate which may have decreased ionized calcium or impaired myocardial function.

FIG 10

FIG 11

It is true that large infusions of blood products containing citrate might decrease the blood level of ionized calcium and adversely affect myocardial function. To test the theory of citrate involvement, Krausz and co-workers[83] subsequently studied nonwashed and washed red blood cells with low 2,3 DPG levels and washed red blood cells with 150% of normal 2,3 DPG. The patients in this study, who were undergoing elective resection of abdominal aneurysms and who were hypothermic with

a body temperature of 35 C throughout the study, were given transfusions of: (a) 4.5 units of washed liquid-stored red blood cells with 10% of normal 2,3 DPG; (b) 4.5 units of nonwashed liquid-stored red blood cells with 10% of normal 2,3 DPG; or (c) 4.5 units of washed previously frozen red blood cells with 150% of normal 2,3 DPG. Blood ionized calcium levels 6 hours postoperatively were not significantly different among the patients in the three groups, even though the nonwashed liquid-stored red cells contained citrate. This may have been due to the relatively small volumes of blood products which were administered and the intervals between transfusion and measurement. Neither were there any significant differences in myocardial function between the washed and nonwashed red blood cell products.

An unexpected observation in this group of elective patients was the 2.2 C fall in intraoperative body temperature to levels below 34 C in some patients. This fall in temperature was accompanied by a 4.9 torr decrease ($p < 0.001$) in in vivo P_{50} in the patients who received nonwashed and washed liquid-stored red blood cell concentrates. A comparable fall in temperature in the patients who received high 2,3 DPG red blood cells was accompanied by an insignificant change in in vivo P_{50}, and in these patients a normal affinity state was maintained during surgery despite the fall in body temperature (Fig 12). Although there FIG 12 did not appear to be any improvement in myocardial function associated with the red blood cells with high 2,3 DPG levels, these patients did exhibit higher in vivo P_{50} values during hypothermia at 35 C, indicating that the red cell 2,3 DPG attenuated the red cell increased affinity for

oxygen which occurs at decreased body temperatures.

More recently Jalonen and associates[84] reported that in the immediate reperfusion period during cardiopulmonary bypass, red blood cells with 150% of normal 2,3 DPG levels and improved oxygen delivery led to a decrease in anaerobic metabolism and lactate production by the heart, without enhancement of cardiac output.

None of these studies show unequivocally that red cells with 150% of normal 2,3 DPG are greatly superior to red blood cells with normal 2,3 DPG levels. The data do suggest, however, that red blood cells with 150% of normal 2,3 DPG may be useful in patients with localized myocardial ischemia. Moreover, there have been no adverse effects associated with the use of high 2,3 DPG red blood cells, and in consideration of the possible beneficial effects, more clinical studies are indicated.

Comparisons of red blood cells with normal to slightly reduced 2,3 DPG and normal affinity for oxygen and red blood cells with 250 to 300% of normal 2,3 DPG and low affinity for oxygen

A number of factors affect the oxygen affinity of red blood cells, including red cell pH, pCO_2 and 2,3 DPG and ATP levels, and temperature.[25,57,85-89] Hypothermia is known to increase the oxygen affinity of red blood cells, and in vitro studies made at the Naval Blood Research Laboratory demonstrated that biochemically modified human red cells with increased 2,3 DPG (150% and 250% of normal) exhibited significantly less affinity for oxygen at 24 C than did red cells with 70% of normal 2,3 DPG. At

15 C, significant attenuation of affinity was associated with the trans-
fusion of red cells with 250% of normal 2,3 DPG but not with red cells
having 150% of normal 2,3 DPG (Figs 13 and 14).[87,88,90]

In a study in which isolated fibrillating dog hearts were perfused
at 24 C alternately with human red blood cells with 80% of normal 2,3 DPG
(nonrejuvenated) and 300% of normal 2,3 DPG (rejuvenated), significantly
greater oxygen consumption, higher coronary sinus partial pressures of
oxygen and carbon dioxide, higher in vitro P_{50} values, and lower arterial
and coronary sinus lactate levels were seen with the rejuvenated red
blood cells.[90] The data from this study suggest that high 2,3 DPG red
cells might protect myocardial tissue in patients undergoing hypoth~~...ic
cardiac operations.

Human red blood cells with 150% of normal 2,3 DPG also have been
perfused through extracorporeal circuits at normothermic temperatures
for 3 hours. The red blood cells had been biochemically modified after
they had reached their outdating period to increase the red cell 2,3 DPG
and ATP levels to 150% of normal prior to freezing. The red cells were
frozen with 40% W/V glycerol and stored at -80 C, thawed, washed, and
stored at 4 C for as long as 3 days prior to use in the extracorporeal
circulation.[91] These red blood cells had excellent posttransfusion
survival and improved oxygen transport function, and produced only minimal
hemolysis.[91] In another study, nonrejuvenated human red blood cells with
80% of normal 2,3 DPG and indated-rejuvenated red cells with 250% of normal
2,3 DPG were perfused in combination with a cardioplegic solution through
a pump oxygenator at a hypothermic temperature of 15 C for 3 hours. The

red cells were stored at 4 C for 7 days, biochemically treated, frozen
with 40% W/V glycerol and stored at -80 C, thawed, washed, and stored
at 4 C for 24 hours prior to perfusion through the extracorporeal circuit.
Both the nonrejuvenated and the indated-rejuvenated red cells had
excellent viability and minimal hemolysis, with no sign of bacterial
contamination, the red blood cells with 80% of normal had normal oxygen
transport function, and the red blood cells with 250% of normal 2,3 DPG
had improved oxygen transport function (Figs 15-17).   FIGS 15-17

In an attempt to protect the myocardium during cardiac surgery,
physicians have used local and systemic hypothermia, cardioplegic
arrest, and intermittent perfusion of the coronary circulation with
cardioplegic solutions with or without blood, although controversy as
to the most effective approach still exists.[92-100] Myocardial oxygen
consumption is reduced during hypothermia, whether because the need
for and availability of oxygen is reduced, the distribution of blood
flow is abnormal, or the consumption of oxygen by the myocardium is
impaired.

Intermittent perfusion of cold cardioplegic solutions through the
coronary circulation is a widely used method of protecting the myo-
cardium during cardiac surgery. Cardioplegic solutions have been quite
effective, but because they are asanguinuous they carry very little
oxygen and therefore may not provide enough oxygen for the myocardium.
For this reason, it has been suggested that a combination of red blood
cells and cardioplegic solution might be more effective.[101] The expected
benefit of additional oxygen delivery to the myocardium expected from a

combination of red blood cells and cardioplegic solution might be offset by an increase in red cell affinity for oxygen occurring during hypothermia which impairs the release of oxygen to tissues. Oxygen release may be hindered further by an elevated pH and a reduced pCO_2, occurring with hypothermia. It has been shown that high 2,3 DPG red cells will attenuate a hypothermia-induced increase in oxygen affinity.[87,88,90]

In a prospective randomized study in humans, the Naval Blood Research Laboratory is studying the comparative effects on myocardial function of the infusions of red blood cells with 80% of normal 2,3 DPG in a cardioplegic solution, red blood cells with 250% of normal 2,3 DPG in a cardioplegic solution, and a cardioplegic solution alone. Two units of washed previously frozen red cells with 80% or 250% of normal 2,3 DPG were diluted with a cardioplegic solution in a separate extracorporeal circuit, and were perfused intermittently in the coronary circulation.

Post-operative ischemia was observed in one of eight patients who received cardioplegic solution alone, in two of eight patients who received a combination of red blood cells with 80% of normal 2,3 DPG and cardioplegic solution, and in two of eight patients who received a combination of red blood cells with 250% of normal 2,3 DPG and cardioplegic solution. No myocardial infarcts were seen in the group receiving cardioplegic solution alone, whereas in each of the two groups receiving red blood cells and cardioplegic solution, two patients suffered myocardial infarcts.

A quantitative creatine phosphokinase (CPK) MB assay showed preoperative CPK levels of 8-18 units for the three groups. Immediately upon cessation of bypass, the levels were 18-32 units, and 24 hours later similar levels were seen in all three groups, with a mean of

56 ± 51 units.

All 24 patients survived surgery, did well clinically, and were discharged from the hospital in an improved condition. Computer analysis of the data has not been completed. If evaluation of oxygen transport and biochemical data reveal no differences among groups, the study will be terminated.

Although red cells with elevated 2,3 DPG levels do decrease the affinity for oxygen that occurs with hypothermia, there are no definitive signs that the intermittent perfusion of these red cells with cardio-plegic solution in the coronary circulation of the hypothermic heart has any beneficial effect.

Red cells with high 2,3 DPG and low affinity for oxygen in patients with arterial hypoxemia

It is important in studying the beneficial effects of 2,3 DPG-enriched red blood cells that potential contraindications also be considered. For instance, are there some instances in which decreased affinity for oxygen associated with high 2,3 DPG red blood cells might impair oxygenation of the red blood cells in the lungs? It is important that the effects of red cell affinity on arterial oxygen content and oxygen tension in hypoxemia be understood.[102-109] A decreased red cell affinity for oxygen will improve arterial hypoxemia due to cyanotic heart disease with right-to-left anatomic shunts or ventilation-perfusion abnormalities with pulmonary shunting (Fig 18).[110-112] In patients with cardiac right-to-left shunts and pulmonary shunting, arterial pO_2 tension, mixed venous pO_2 tension,

FIG 18

and coronary sinus pO_2 tension will increase if the red cell affinity for oxygen is decreased, provided that the inspired ambient oxygen tension is adequate to maintain an arterial pO_2 tension of greater than 40 mm Hg, and in these patients red blood cells with 150 to 200% of normal 2,3 DPG and low affinity for oxygen are indicated.[63,112] Proctor and associates[113-115] have reported clinical improvement in patients with severe pulmonary insufficiency following the transfusion of human red cells with elevated 2,3 DPG levels.

Blood products for cardiac surgery

Today there is an increased requirement for blood products for cardiac surgery in which extracorporeal bypass is utilized.[116,117] Blood products are given to provide optimum oxygen to the tissues, especially to the heart and brain, for maintenance or restoration of normal hemostasis, and for optimum protection against infection. The patient's state of health and the length of cardiopulmonary bypass determine which blood products are required, whether oncotic, clotting, and opsonic proteins, platelets, or red cells; the cardiopulmonary bypass procedure may adversely affect the viability and function of these blood components. Abnormalities in blood coagulation[118-131] and hemolysis of red cells[132,133] may occur during bypass surgery. The heparin used to anticoagulate the patient's blood during bypass and the citrate used in the anticoagulant in which the blood product is stored both may adversely affect platelet function.[134-136] Moreover, hypothermia[137,138] and anesthesia[139] may affect the hemostatic mechanism; drugs such as aspirin[140] may affect platelet function, and

heparin per se[141-144] may produce thrombocytopenia.

The bleeding diathesis during and following extracorporeal bypass surgery is a complicated process which may be affected in any number of ways, e.g., the failure of the surgeon to suture severed blood vessels, by the length of the bypass procedure, the failure to neutralize administered heparin, the excessive administration of protamine sulfate, a decrease in level of clotting proteins, a reduction in platelet number and abnormalities of platelet function, disseminated intravascular coagulation, or by fibrinolysis.

Potential risks associated with donor blood products such as post-transfusion hepatitis and isoimmunization can be reduced by collecting blood from the patient prior to elective surgery, by collecting intra-operative blood from the patient during surgery and shed blood after surgery from thoracic drainage sites.[25,145-151] It is recommended though that shed blood be washed prior to reinfusion to prevent disseminated intravascular coagulation and a bleeding diathesis.[152]

Hemodilution with crystalloid-colloid solutions to produce acute normovolemic anemia has been utilized during cardiopulmonary bypass operations to minimize or eliminate the need for blood products.[153-167] Reports that moderate hemodilution produces no deleterious effects[168-170] are encouraging, though not substantiated by physiologic data.

Albumin also has been utilized during extracorporeal bypass for the purpose of maintaining plasma oncotic pressure so as to minimize the accumulation of edema fluid in the tissue. Although albumin has also been shown to protect platelet function during cardiopulmonary

bypass,[171] its disadvantages appear to outweigh its advantages. Albumin has been shown to adversely affect the heart,[23] lung,[28,29] kidney,[49,50] immunologic system,[51] and clotting function.[46-48] Mannitol reportedly reduces myocardial edema during cardiopulmonary bypass surgery,[172] whereas the colloid solution, plasma protein fraction, is not recommended because it may produce severe hypotension during extracorporeal bypass.[173-179]

Numerous blood substitutes and blood products have been used to prime the extracorporeal circuit: crystalloid solutions, colloid solutions, and blood products, osmotic diuretic agents such as mannitol, and buffer solutions such as bicarbonate. The pump may be primed with crystalloid-colloid solutions and hemodilution, crystalloid-colloid solutions and washed previously frozen red cells alone[180] or in combination with liquid-stored blood products,[181] crystalloid-colloid solutions in combination with liquid-stored red blood cell concentrates or stored whole blood, or crystalloid-colloid solutions in combination with fresh whole blood.

Numerous studies have shown no differences in platelet counts or platelet function, white cell count, clotting measurements, oxygen transport, microaggregates, red cell function, hemodynamics, pulmonary function, blood products used, or fluid balance, whether a membrane or bubble oxygenator was utilized during extracorporeal bypass.[182-190] It may very well be true that there are no differences with these two types of oxygenators; nevertheless, studies should be made to evaluate the sensitivity of the measurements used. Other factors associated with the surgery also may be involved which have a greater effect on blood

trauma than the oxygenator. Cardiotomy suction produces far more trauma to blood than does the membrane or the bubble oxygenator, and suction damage can easily mask any difference between oxygenators.[191,192]

Coagulation tests, platelet counts, and platelet function tests during and after cardiopulmonary bypass surgery

Plasma coagulation protein levels usually are decreased during extracorporeal bypass. Coagulation factor levels about 30% of normal usually are adequate for all factors, except for Factor V which shows adequate hemostasis at levels of 10-15%.[137] Abnormal bleeding following cardiopulmonary bypass generally is not due to reductions in the levels or function of coagulation factors.[130,131,137] Moreover, factors such as excessive anticoagulation with heparin, excessive neutralization with protamine sulfate, qualitative defects in the polymerization of fibrin, increased fibrinolytic activity, or the effects of fibrin-fibrinogen degradation products on coagulation do not usually produce bleeding following cardiopulmonary bypass.[126,130,131,137]

Postoperative hemorrhage in patients undergoing cardiopulmonary bypass may be due to defective platelet plug formation related to abnormalities of platelet function.[193-199] The degree of impairment in platelet function is usually proportional to the duration of bypass and to the level of hypothermia.[137] The prostaglandin compounds, PGE_1 and PGI_2, have been utilized during extracorporeal bypass to maintain platelet number and function.[200-202] The platelet dysfunction is rapidly reversible in most patients, although clinical bleeding will

occur in patients with a persistent functional platelet defect. The standardized template bleeding time detects patients at risk of serious postoperative bleeding.[137,194] Platelet concentrate transfusions are indicated to treat a bleeding diathesis in a patient with a platelet count below 50,000/ul, as well as for patients with a bleeding diathesis and a bleeding time of greater than 20 minutes when the platelet count exceeds 100,000/ul. Bleeding time is a better indicator of the need for platelet transfusion than the platelet count itself, and measurements of both platelet count and bleeding time should be made in patients who fail to stop bleeding after cardiopulmonary bypass surgery. No currently available preoperative laboratory test of hemostatic function can accurately predict coagulopathies resulting from cardiopulmonary bypass.[130]

Blood products recommended during and after cardiopulmonary bypass surgery

Red blood cell concentrates with normal or improved oxygen transport function have been shown to provide the best results in patients undergoing cardiopulmonary bypass, and should be used instead of fresh whole blood or stored whole blood. Red blood cell concentrates stored in the liquid state at 4 C for 3 to 5 days with hematocrit values of 80 V% usually have normal 2,3 DPG levels, and liquid-stored red blood cells can be biochemically treated to elevate 2,3 DPG. Red cells with elevated 2,3 DPG levels attenuate the increased red cell affinity for oxygen that occurs during hypothermia and provide higher oxygen tension in the tissues. Whether or not the tissues utilize the increased oxygen has not yet been determined. Nevertheless, we believe that the safest course to follow

for patients undergoing cardiopulmonary bypass surgery is to use red cells with high 2,3 DPG levels and decreased oxygen affinity. Crystalloid solutions, not colloid solutions such as albumin and plasma protein fraction, are recommended as the volume expander for the pump prime.

Platelet transfusions should not be administered during extra-corporeal bypass. However, platelet transfusions should be used to treat the bleeding diathesis after bypass associated with a significant thrombocytopenia (less than 50,000 platelets/ul) or with bleeding accompanied by a prolonged bleeding time and a platelet count of 100,000 or greater per ul. Six to 8 units of fresh platelets should be administered. When it is necessary to administer preserved platelets, it is important that the circulation and function of these platelets are known.[203-212] Data have shown that platelets stored at 22 ± 2 C have impaired function and require periods of time in the circulation to restore function.[25,213] Platelets stored at 4 C for 24 hours have been shown to have better function than platelets stored at room temperature $(22 \pm 2$ C) for 24 hours.[214-216] No studies have yet been made in patients undergoing cardiopulmonary bypass to measure the function of platelet concentrates stored at room temperature $(22 \pm 2$ C) for 5 days.[217-219] Patients with clinical bleeding and severe dilutional coagulopathies are best treated with 4 to 6 units of fresh frozen plasma, although there are no indications for the routine use of fresh frozen plasma during extracorporeal bypass surgery.[220,221]

Stored whole blood and plasma stored at 4 C have recently been

shown to give rise to impairment in oxygen consumption by isolated
skeletal muscle,[30,31] and increased pulmonary permeability,[24] and there-
fore are not recommended during cardiopulmonary bypass surgery. As
regards the use of plasma opsonic protein, this is still in the
speculative stage.[222-227]

Summary

The oxygen transport function of preserved red cells transfused to anemic patients who have heart disease is critical. Patients with heart disease should be given red cells with normal 2,3 DPG and normal affinity for oxygen instead of low 2,3 DPG red cells. Our studies suggest that red cells with high 2,3 DPG (150 to 200% of normal) and low affinity for oxygen are the best form of transfusion therapy for anemic patients, especially those with congestive heart failure. It may even prove useful to use 2,3 DPG-enriched red cells in patients with patchy myocardial ischemia and, at any rate, it can do no harm. High 2,3 DPG red blood cells also are recommended in patients with right-to-left cardiac shunts and pulmonary shunts, provided that the inspired ambient oxygen tension is adequate to maintain an arterial pO_2 tension of greater than 40 mm Hg.

Blood products utilized during extracorporeal bypass surgery should ensure optimum oxygen delivery to tissue and maintain or restore normal hemostasis, and red cells with 250% to 300% of normal 2,3 DPG and low affinity for oxygen given in combination with crystalloid solution will do this. Red cells with elevated 2,3 DPG levels do ensure optimum delivery of oxygen to tissue, especially during hypothermia, although it cannot be stated definitely whether or not they reduce myocardial damage.

A postoperative bleeding diathesis following cardiopulmonary bypass due to a decrease in platelet number and to abnormalities of platelet function should be treated with platelet transfusions. Although a bleeding diathesis as a result of dilutional coagulopathies is rare,

severe dilutional coagulopathies should be treated with fresh frozen plasma.
However, routine use of fresh frozen plasma following cardiopulmonary
bypass is not recommended.

Acknowledgments

Fig 1 -- The effect of anemia on cardiac index and red cell 2,3 DPG level.
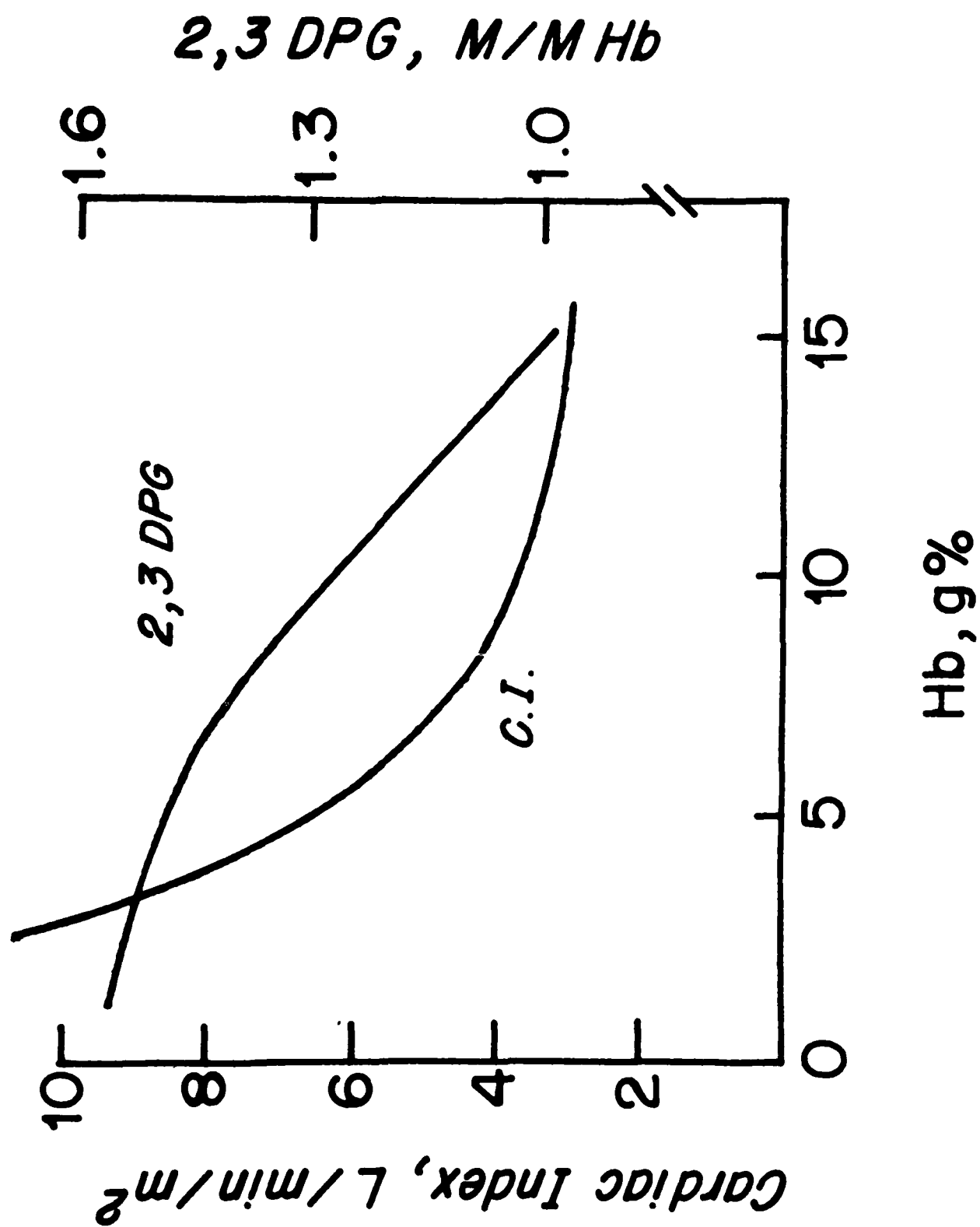(Reproduced with permission from Finch CA and Lenfant C, N Engl J Med 1972;
286:412).

Fig 2 -- The 2,3 DPG levels in red blood cells stored at 4 C in citrate-
phosphate-dextrose as whole blood with a hematocrit value of 40 V%, or as
a red blood cell concentrate with a hematocrit value of 70-80 V% or of
greater than 90 V%. Neither the whole blood nor the red blood cell concen-
trate was mixed during liquid storage at 4 C. (Reproduced with permission
from Valeri CR, Surgical Rounds 1981;4:41).

Legend:
- ● CPD Whole Blood with Hct. of 40 V%
- ○ CPD RBC Concentrate with Hct. of 70-80 V%
- × CPD " " " >90 V%

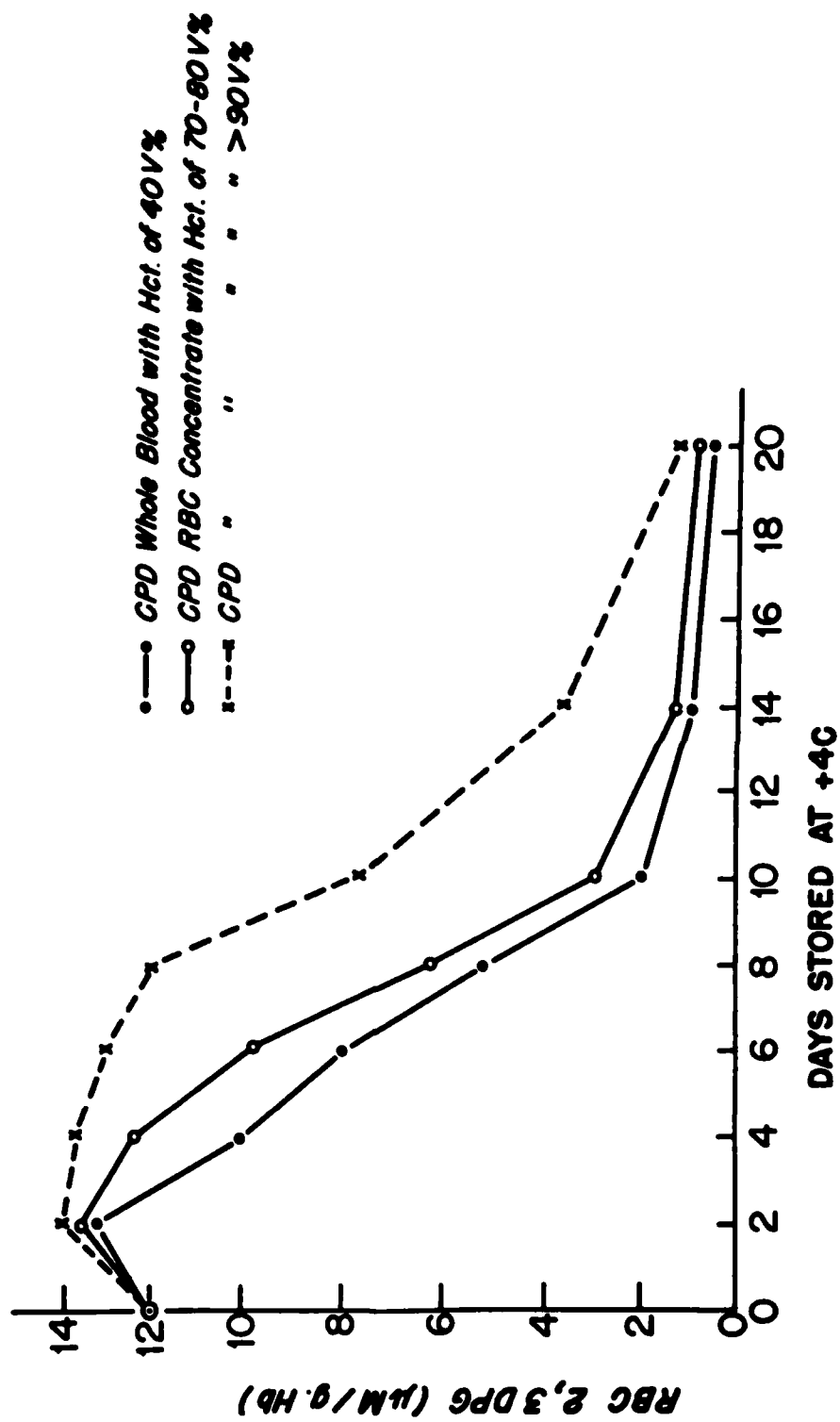DAYS STORED AT +4C

RBC 2,3 DPG (μM/g. Hb)

Fig 3 -- The 2,3 DPG levels in red blood cells after storage in CPDA-1
at 4 C as whole blood or as a red blood cell concentrate with a hemato-
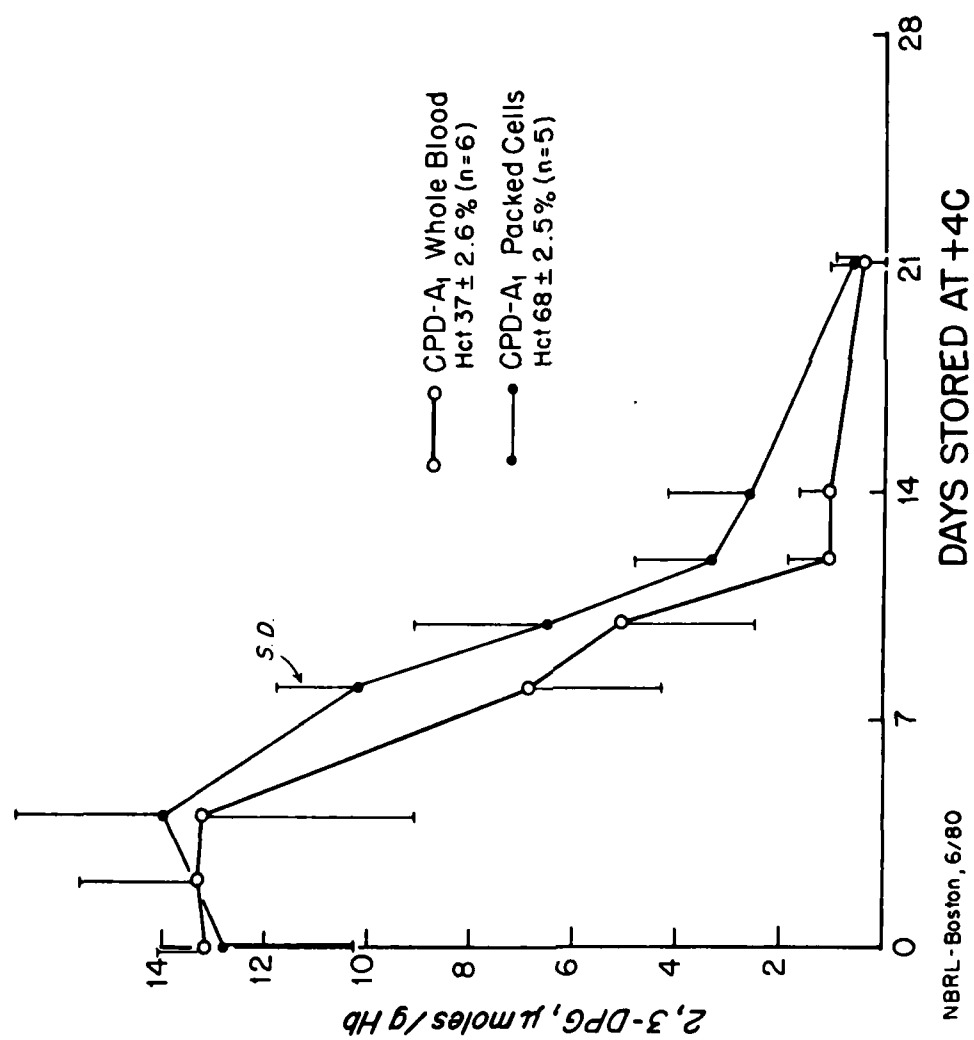crit value of 70 V%.

2,3-DPG, μmoles/g Hb

DAYS STORED AT +4C

CPD-A₁ Whole Blood
Hct 37 ± 2.6% (n=6)

CPD-A₁ Packed Cells
Hct 68 ± 2.5% (n=5)

S.D.

NBRL-Boston, 6/80

Fig 4 -- The 2,3 DPG levels of red cell concentrates stored at 4 C in CPD,
CPDA-1, CPDA-2 or CPDA-3 (Reproduced with permission from Valeri CR,
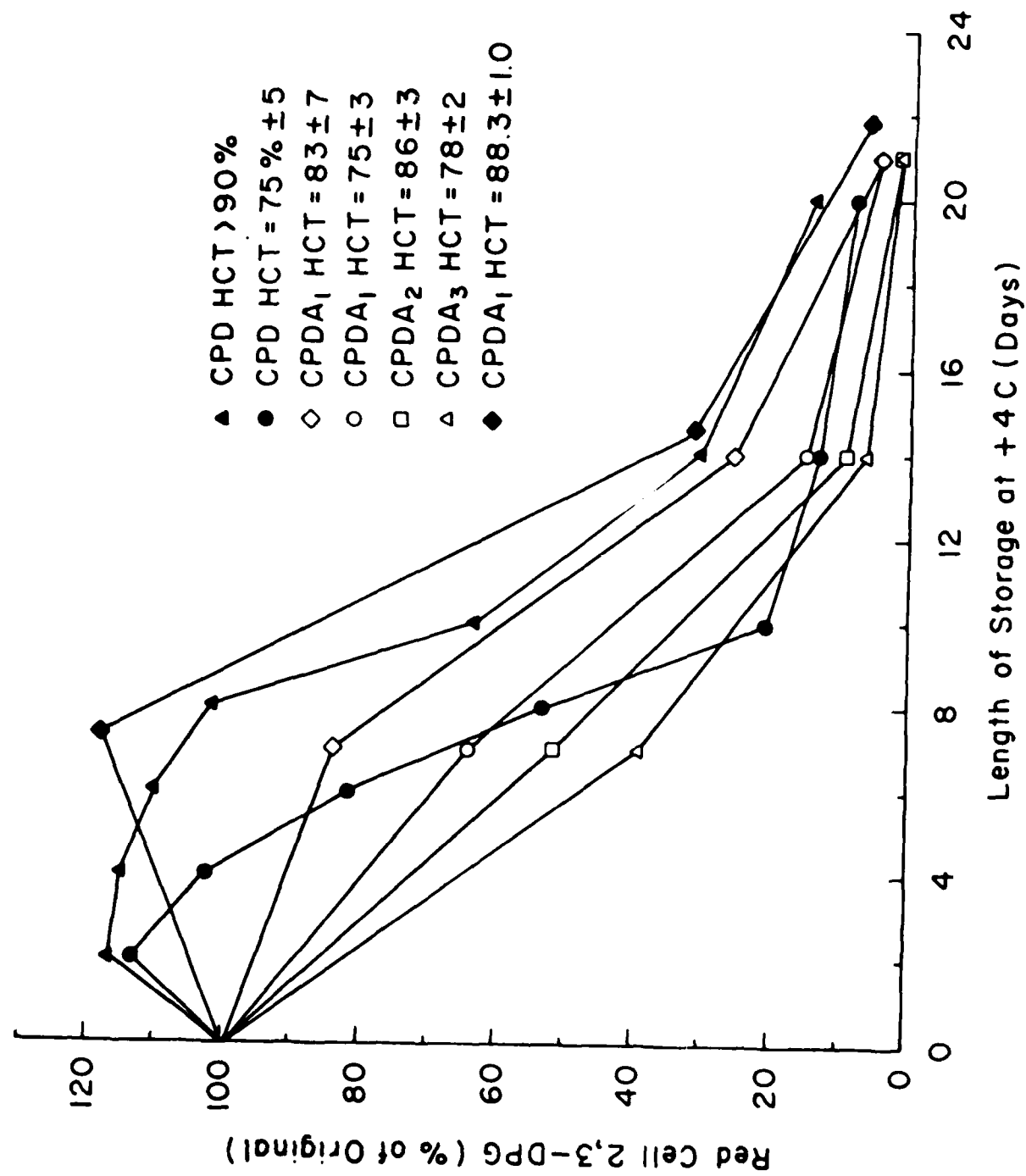Crit Rev Clin Lab Sci, in press).

Legend (reading top to bottom):
- ▲ CPD HCT > 90%
- ● CPD HCT = 75% ± 5
- ◇ CPDA₁ HCT = 83 ± 7
- ○ CPDA₁ HCT = 75 ± 3
- □ CPDA₂ HCT = 86 ± 3
- △ CPDA₃ HCT = 78 ± 2
- ◆ CPDA₁ HCT = 88.3 ± 1.0

X-axis: Length of Storage at +4 C (Days)

Y-axis: Red Cell 2,3-DPG (% of Original)

Fig 5 -- The ATP and 2,3 DPG levels in red cell concentrates after storage

as whole blood in ACD, CPD, ACD-supplemented with 0.5 mM adenine, or CPD

supplemented with 0.25, 0.50, and 0.75 mM adenine. (Reproduced with

permission from Hogman CF, Akerblom O, Arturson G, deVerdier C, Kreuger A,

and Westman M. In: Greenwalt TJ and Jamieson GA, eds. The Human Red Cell

In Vitro. New York: Grune & Stratton, 1974:221).

mole/mole Hb

ATP

2,3 - diphosphoglycerate (DPG)

.3

.2

.1

1.0

.8

.6

.4

.2

7   14   21   28   35   D.

∘—∘ CPD
●—● CPD-ad. 0.25 mM
⊶ CPD-ad. 0.50 mM
●—● CPD-ad. 0.75 mM
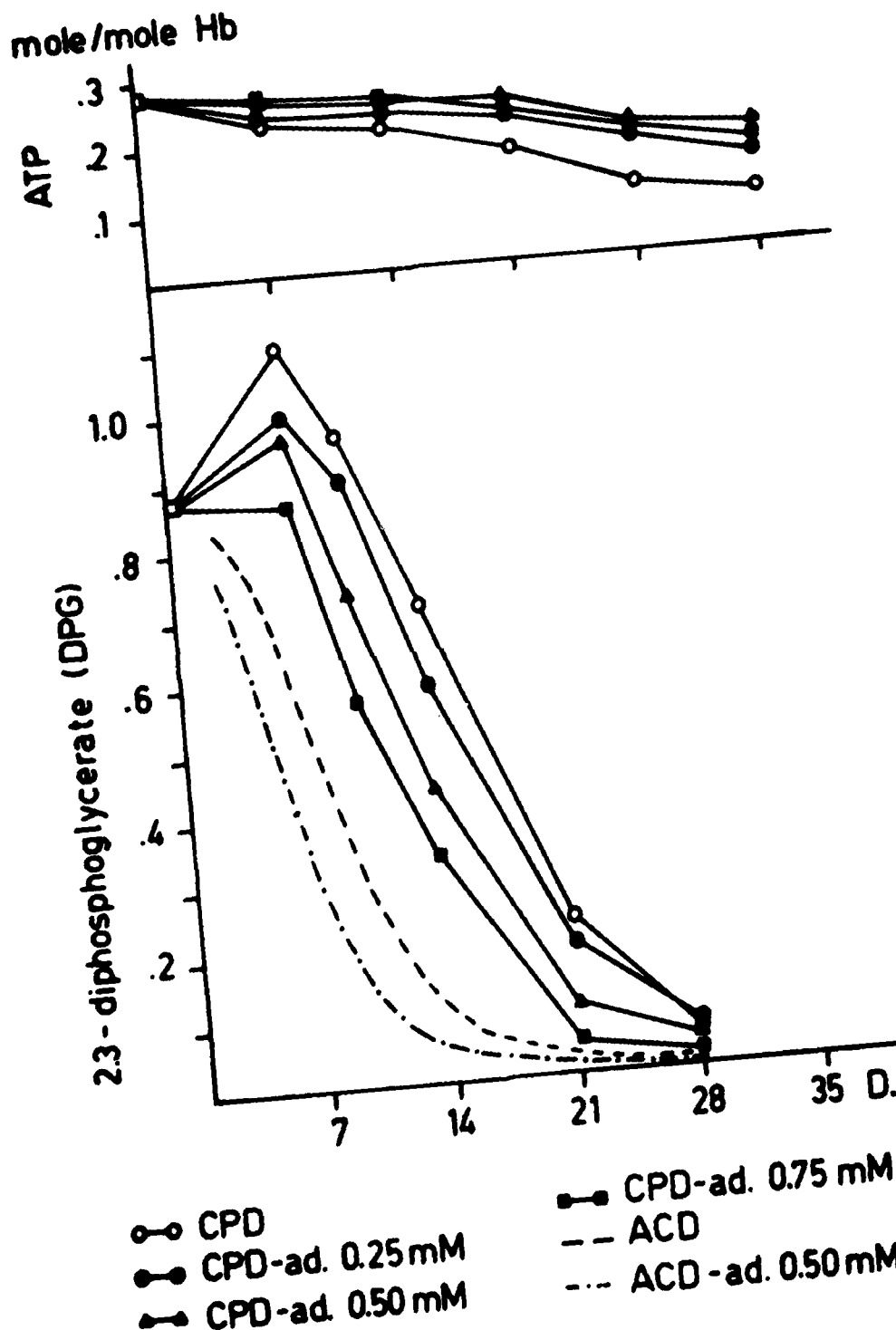— — ACD
—·—· ACD-ad. 0.50 mM

Fig 6 -- Red cell 2,3 DPG and ATP levels, and P_{50} values for red blood cell concentrates with hematocrits of 80 $\pm$ 5 V%, stored at 4 C in CPD for 6 to 8 days or for 25 days, biochemically treated with PIPA or FRES, frozen with 40% W/V glycerol in the original polyvinylchloride collection bag at -80 C, thawed, and washed. (Reproduced with permission from Valeri CR, Crit Rev Clin Lab Sci, CRC Press, in press).
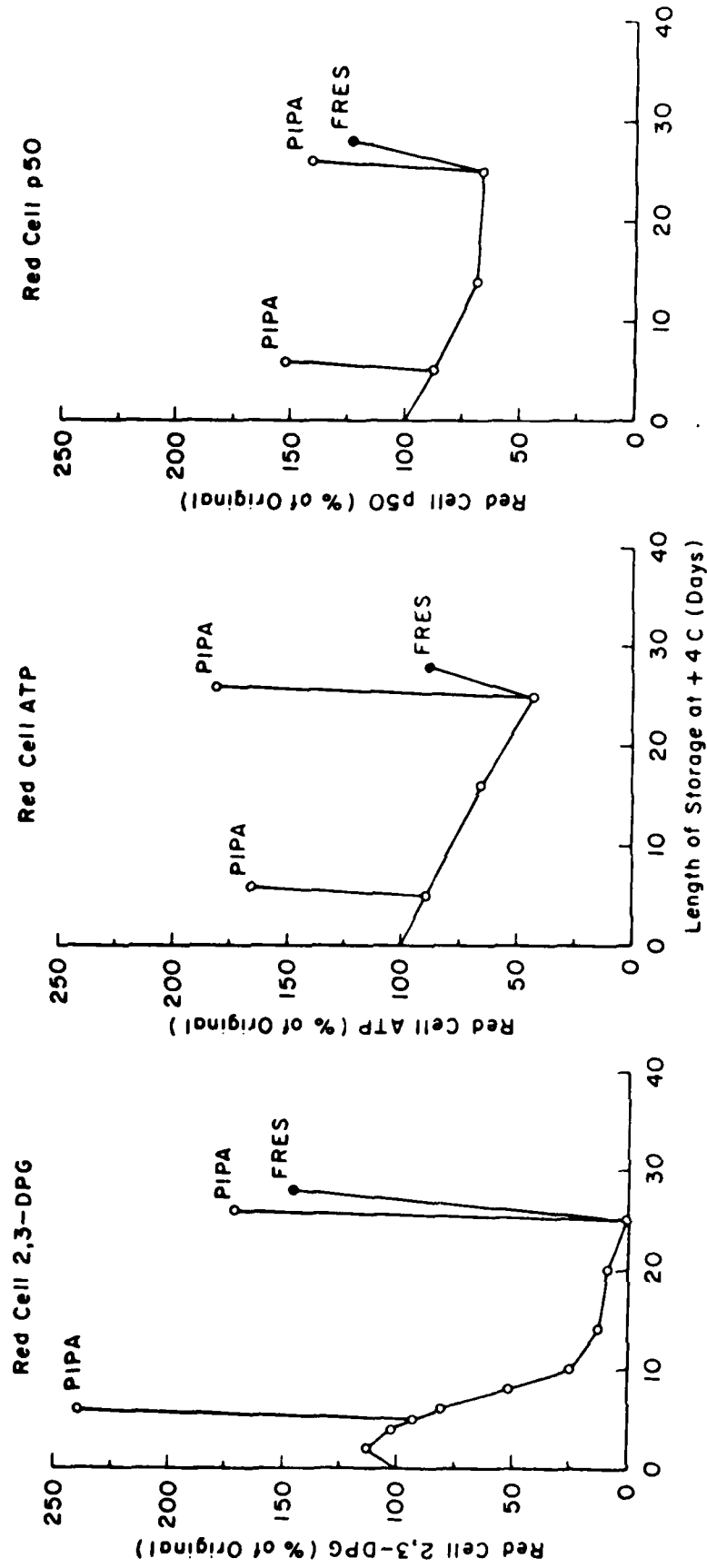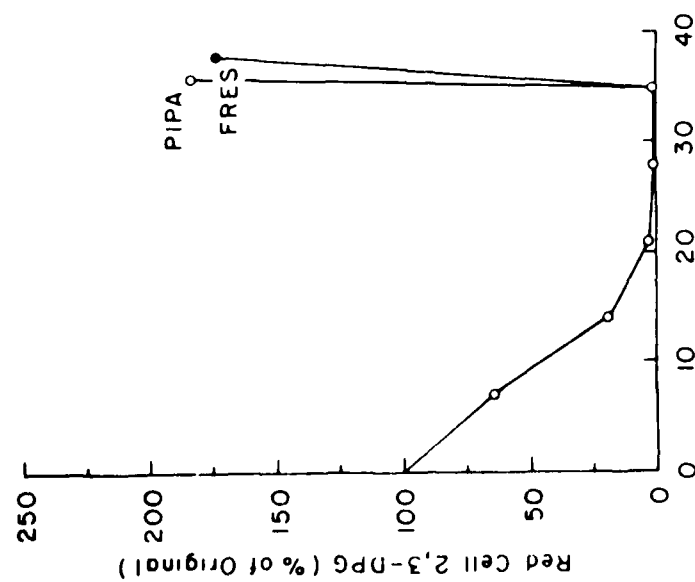
Red Cell 2,3-DPG   Red Cell ATP   Red Cell p50

Length of Storage at + 4 C (Days)

Fig 7 -- Red cell 2,3 DPG and ATP levels, and P_{50} values for red blood cell concentrates with hematocrits of 80 ± 5 V%, stored at 4 C in CPDA-1 for 35 days, biochemically treated with PIPA or FRES, frozen with 40% W/V glycerol in the original polyvinylchloride collection bag at -80 C, thawed, and washed. (Reproduced with permission from Valeri CR, Crit Rev Clin Lab Sci, CRC Press, in press).

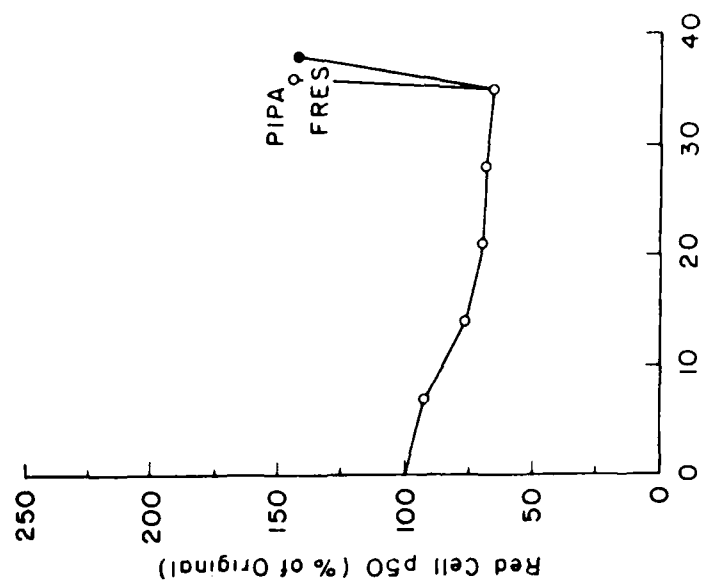Red Cell 2,3-DPG

Red Cell ATP
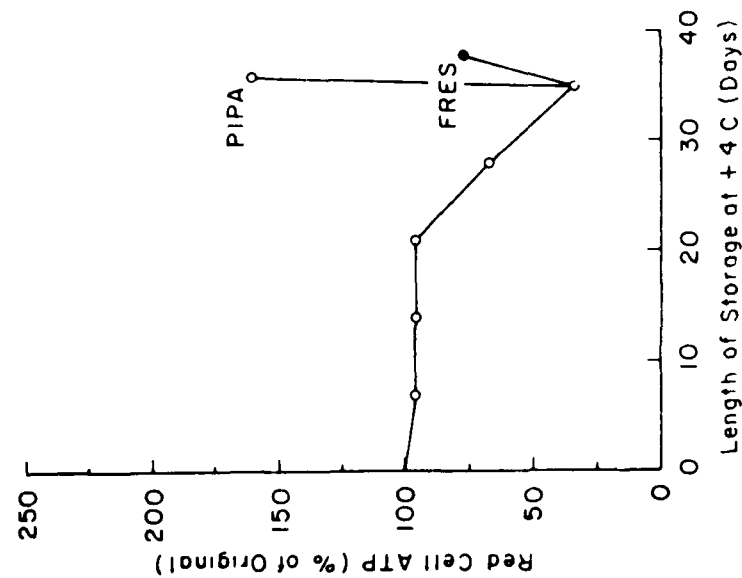
Red Cell p50

Fig 8 -- Freeze-thaw-wash recovery in vitro, ^{51}Cr 24-hour posttransfusion survival, index of therapeutic effectiveness and length of storage at 4 C, of red blood cell concentrates (hematocrit value of 80 $\pm$ 5 V%) collected in CPD or CPDA-1, biochemically modified with PIPA or FRES, frozen with 40% W/V glycerol in the primary collection bag and stored at -80 C, washed in the Haemonetics Blood Processor 115 or the IBM Blood Processor 2991, and stored at 4 C for 24 hours in the final wash solution of 0.9% NaCl-0.2% glucose-40 mg% inorganic phosphorus (pH 6.8) or 0.9% NaCl-0.2 glucose (pH 5.0). (Reproduced with permission from Valeri CR, Crit Rev Clin Lab Sci, CRC Press, in press).
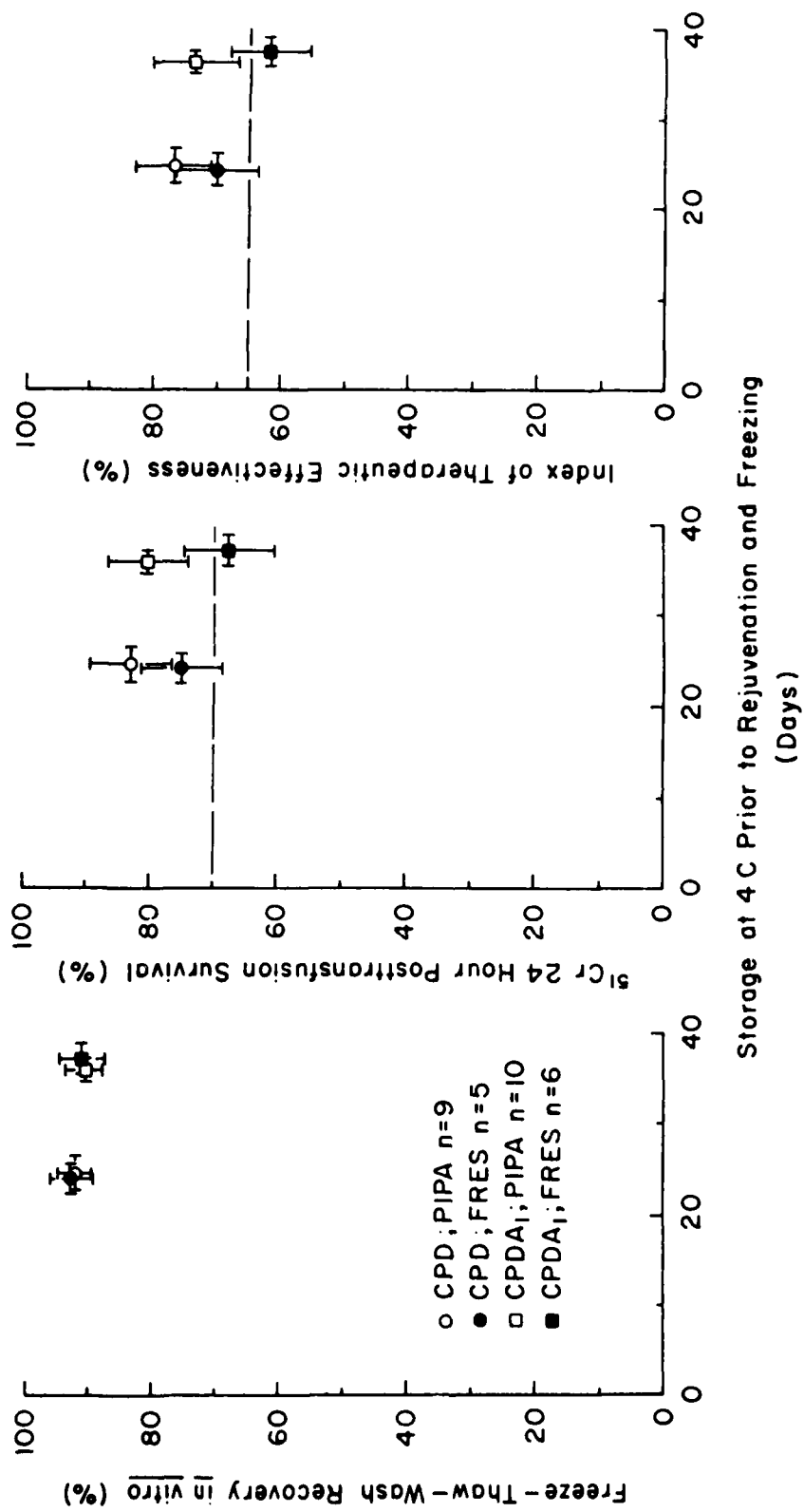
Index of Therapeutic Effectiveness (%)

⁵¹Cr 24 Hour Posttransfusion Survival (%)

Freeze-Thaw-Wash Recovery in vitro (%)

o CPD; PIPA n=9
● CPD; FRES n=5
□ CPDA₁; PIPA n=10
■ CPDA₁, FRES n=6

Storage at 4 C Prior to Rejuvenation and Freezing
(Days)

Fig 9 -- Theoretical red blood cell mass and ^{51}Cr-measured red blood cell

mass in the recipient prior to and 24 hours after the transfusions.

The in vivo P_{50} value, hematocrit, and red cell 2,3 DPG level are reported

prior to and following the transfusions of red cells with 150% of normal

2,3 DPG. The red cell mass 24 hours after transfusion is the sum of the

red cell mass of the recipient prior to transfusion and the donor red

cell mass in the circulation 24 hours after transfusion which is the

product of the red cell mass of donor hemoglobin transfused multiplied

by the 24-hour posttransfusion survival measured by the automated

differential agglutination (ADA) procedure. (Reproduced with permission

from Valeri CR, Zaroulis CG, Vecchione JJ, et al. Transfusion 1980;20:269).
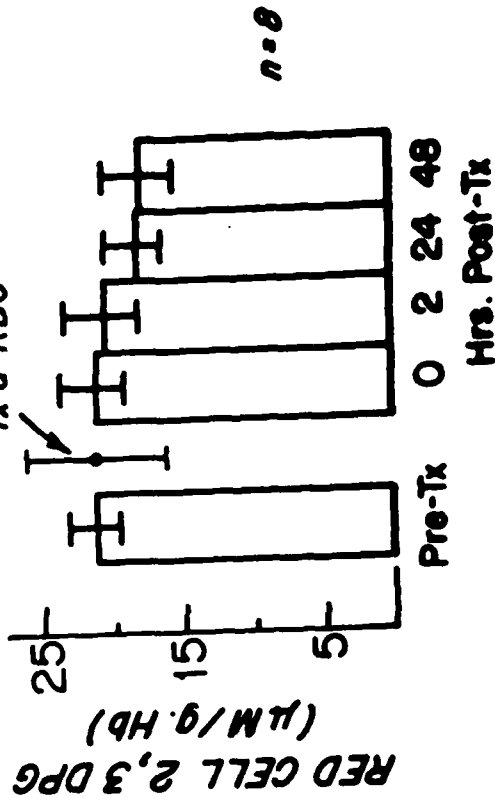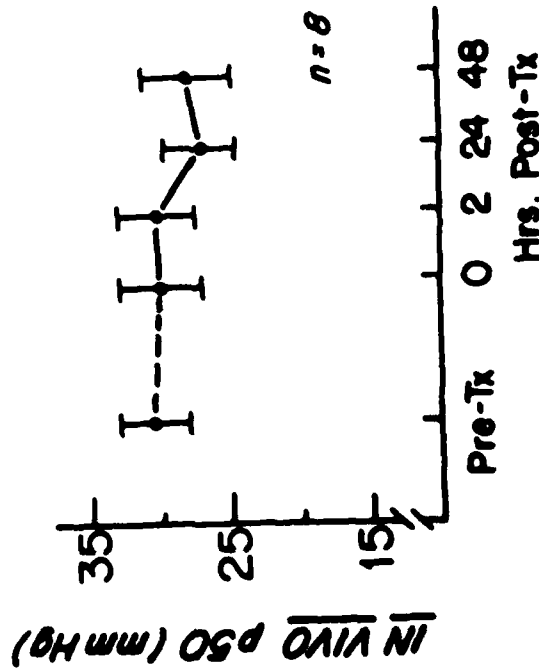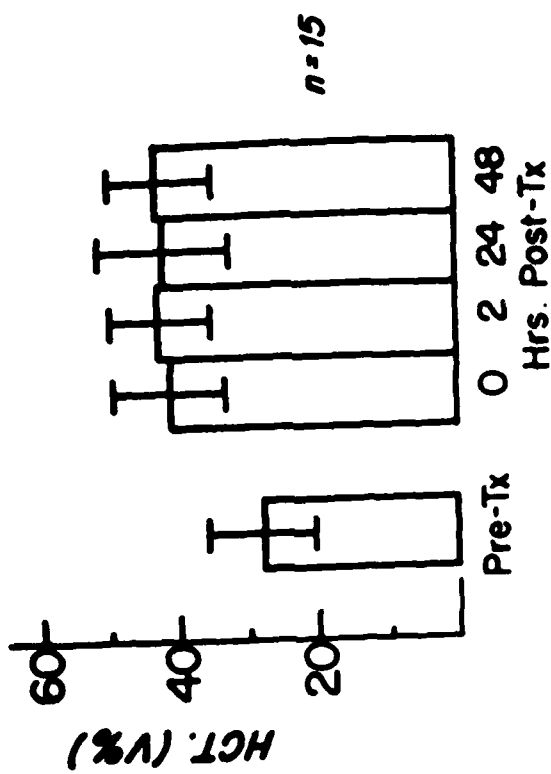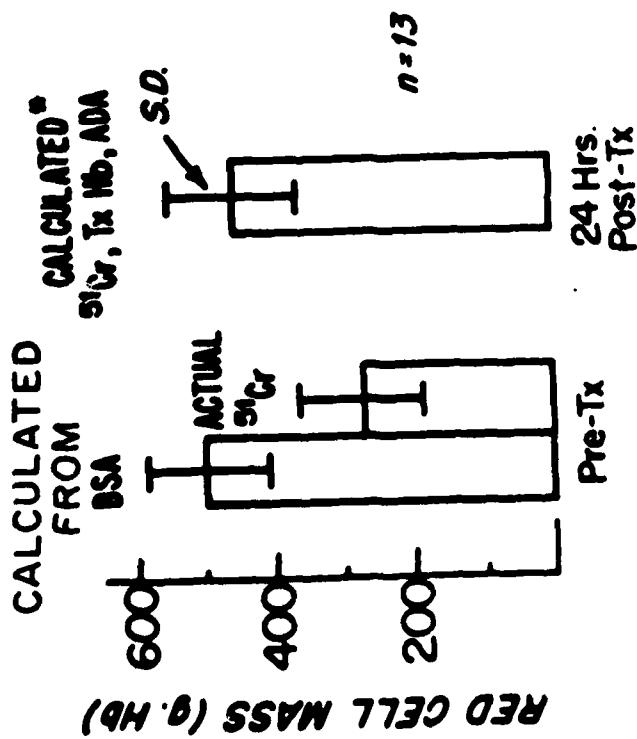
Fig 10 -- Transfusions of 2,3 DPG-enriched red blood cells resulted in higher levels of 2,3 DPG and plasma inorganic phosphorus and an increased in vivo P_{50} value. Oxygen consumption was increased in patients given red blood cells high in 2,3 DPG in the period immediately after cardiopulmonary bypass. Both the cardiac index and arteriovenous oxygen content difference were elevated at this time. (Reproduced with permission from Dennis RC, Hechtman HB, Berger RL, Vito L, Weisel RD, and Valeri CR, Ann Thorac Surg 1978;26:20).

Preserved Red Cells with ~70% of Normal 2,3 DPG

" " " ~150% " " "

* p<0.05
** p<0.02
**** p<0.002

p50 IN VIVO (mm Hg) Pulm. Art.

RED CELL 2,3 DPG (μ moles/g. Hb)

PLASMA INORGANIC PHOSPHORUS (mg %)

O₂ CONSUMPTION (ml /min/m²)

CARDIAC INDEX (L./min · m²)

A-V DIFF. O₂ CONTENT (ml /g. Hb)

HOURS

ON BYPASS

PRE

Mean ± S.D.
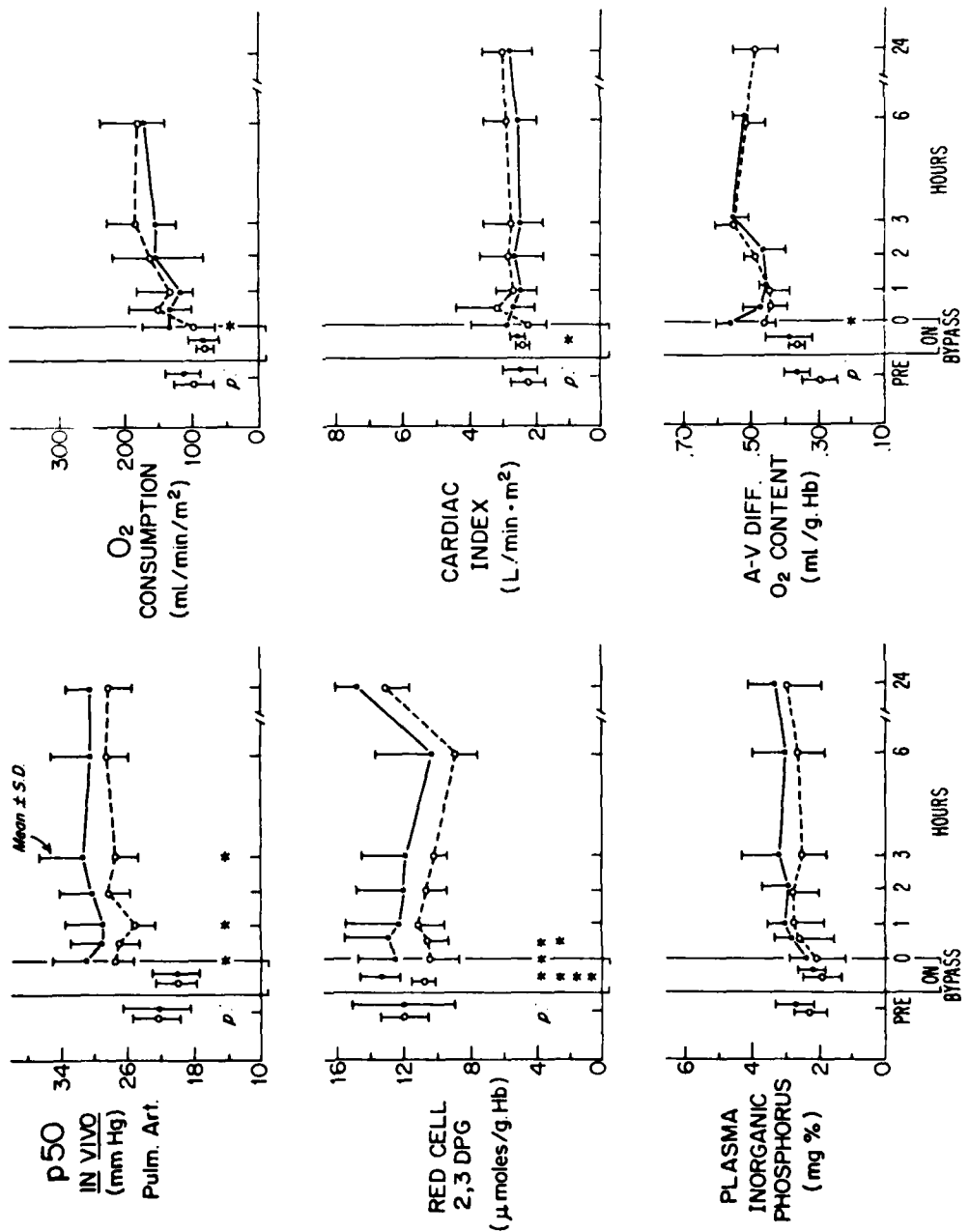
Fig 11 -- Cardiac output and the filling pressure of the left ventricle associated with volume loading prior to, immediately following, and 24 hours after cardiopulmonary bypass. During extracorporeal bypass for coronary artery bypass surgery, these patients with coronary artery disease received red blood cells with either 70% or 150% of normal 2,3 DPG levels. (Reproduced with permission from Dennis RC, Hechtman HB, Berger RL, Vito L, Weisel RD, and Valeri CR, Ann Thorac Surg 1978;26:22).

VOLUME LOADING FUNCTION CURVES
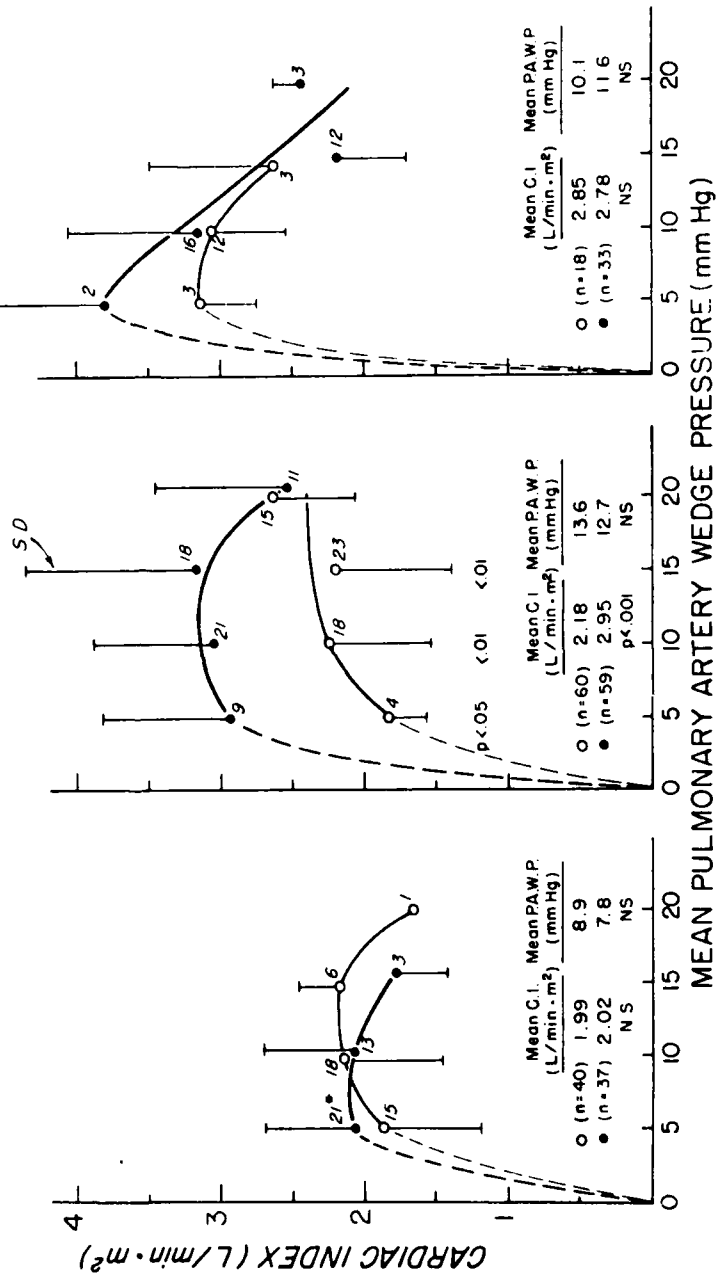
PRESERVED RED CELLS WITH:
○——○ ~70% of Normal 2,3 DPG
●——● ~150% of " "

CARDIAC INDEX (L/min·m²)

MEAN PULMONARY ARTERY WEDGE PRESSURE (mm Hg)

* No. of Observations at each Range of Wedge Pressure

PRE - BYPASS

	Mean C.I. (L/min·m²)	Mean PAW.P. (mmHg)
○ (n=40)	1.99	8.9
● (n=37)	2.02	7.8
	NS	NS

JUST OFF BYPASS

	Mean C.I (L/min·m²)	Mean PAWP (mmHg)
○ (n=60)	2.18	13.6
● (n=59)	2.95	12.7
	p<.001	NS

p<.05   <.01   <.01

S.D

24 HRS. OFF BYPASS

	Mean C.I. (L/min·m²)	Mean PAWP (mm Hg)
○ (n=18)	2.85	10.1
● (n=33)	2.78	11.6
	NS	NS

Fig 12 -- In vitro P_{50} decreased significantly 6 hours after surgery for
abdominal aneurysm resection in the patients who received nonwashed liquid-
stored red cell concentrates ($p < 0.005$) and washed liquid-stored red cell
concentrates ($p < 0.001$), but not in patients who received washed previously
frozen red cells with 150% of normal 2,3 DPG levels. Intraoperatively
body temperature decreased by more than 2.0 C in the three groups of
patients ($p < 0.001$). This was followed by falls of in vivo P_{50} in the patients
who received nonwashed packed red cells ($p < 0.001$) and washed red cells
($p < 0.05$), while there was no change in the patients who received washed
previously frozen red cells with 150% of normal 2,3 DPG. The postoperative
rise in body temperature and fall in pH in the three groups of patients was
accompanied by a significant elevation of the in vivo P_{50} above preoperative
values in the patients who received high 2,3 DPG red cells ($p < 0.001$).
(Reproduced with permission from Krausz MM, Dennis RC, Utsunomiya T, et al,
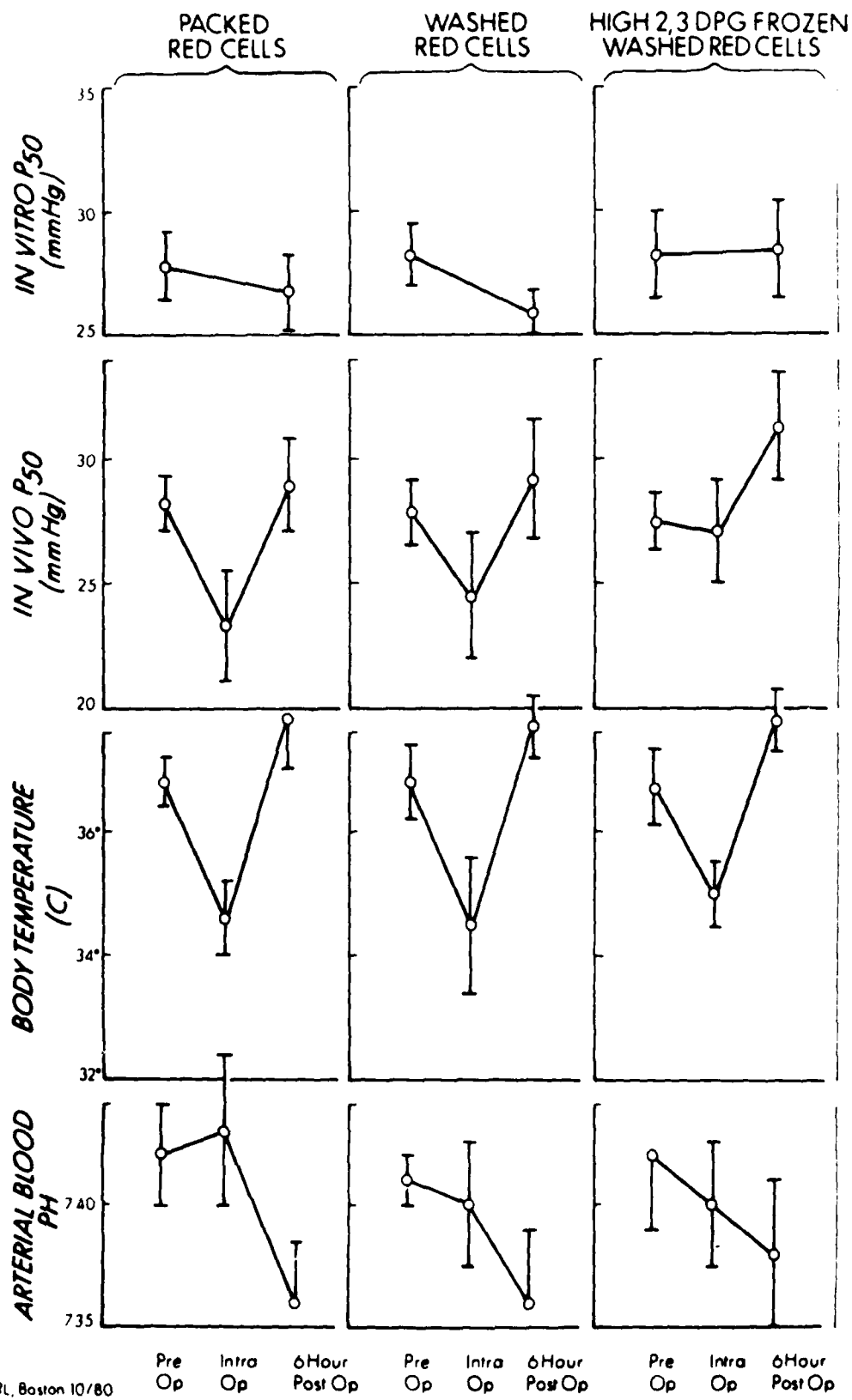Ann Surg 1981;194:620).

PACKED RED CELLS   WASHED RED CELLS   HIGH 2,3 DPG FROZEN WASHED RED CELLS

IN VITRO P50 (mmHg)

IN VIVO P50 (mm Hg)

BODY TEMPERATURE (C)

ARTERIAL BLOOD PH

Pre Op   Intra Op   6 Hour Post Op   Pre Op   Intra Op   6 Hour Post Op   Pre Op   Intra Op   6 Hour Post Op

NBRL, Boston 10/80

Fig 13 -- Red cell 2,3 DPG and ATP levels in non-rejuvenated and rejuvenated red blood cells after cryopreservation. Three units of red blood cells were stored in CPD at 4 C for about 7 days and then pooled. The 3-unit pool was divided into three equal portions: 1 portion was not rejuvenated (70% normal 2,3 DPG); 1 portion was rejuvenated with PIGPA Solution A (150% normal 2,3 DPG); and the third portion was rejuvenated with PIGPA Solution B (250% normal 2,3 DPG). Each portion was glycerolized to a final concentration of 40% W/V glycerol and then divided into three 130 ml aliquots. Each of the nine aliquots was frozen separately and stored at -80 C, thawed, and washed prior to study. (Reproduced with permission from Valeri CR, Yarnoz M, Vecchione JJ, et al, Ann Thorac Surg 1980;30:531).

Red Cells Stored at 4C for ~7 Days (Control)

Red Cells Stored at 4C for ~7 Days & Then Treated with Sol. A

Red Cells Stored at 4C for ~7 Days & Then Treated with Sol. B

RED CELL 2,3 DPG

RED CELL ATP

$(n=3)$

$(n=3)$

Mean ± S.D.

$(\mu\,moles/g.\,Hb)$
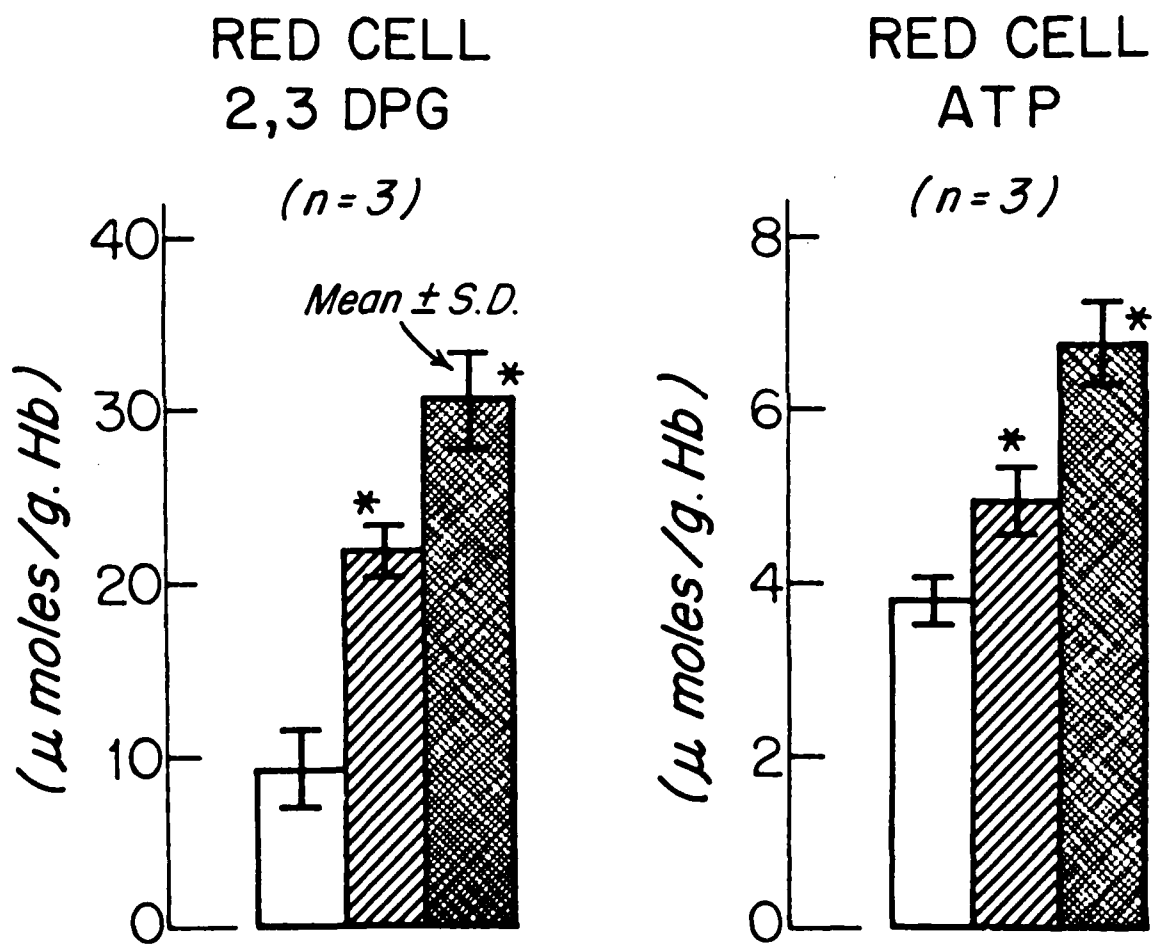
*$p < 0.05$ (Control vs. Sol. A or Sol. B)

Fig 14 -- The P_{50} values of washed previously frozen red blood cells with 70% of normal, 150% of normal, or 250% of normal 2,3 DPG, measured at 10 C, 15 C, 24 C, and 37 C. (Reproduced with permission from Valeri CR, Yarnoz M, Vecchione JJ, et al, Ann Thorac Surg 1980;30:531).

IN VITRO p50 (mmHg)

Red Cells Stored at 4C for ~7 Days (Control)

Red Cells Stored at 4C for ~7 Days & Then Treated with Sol. A

Red Cells Stored at 4C for ~7 Days & Then Treated with Sol. B

Mean ± S.D. n=3

TEMPERATURE

10C 15C 24C 37C
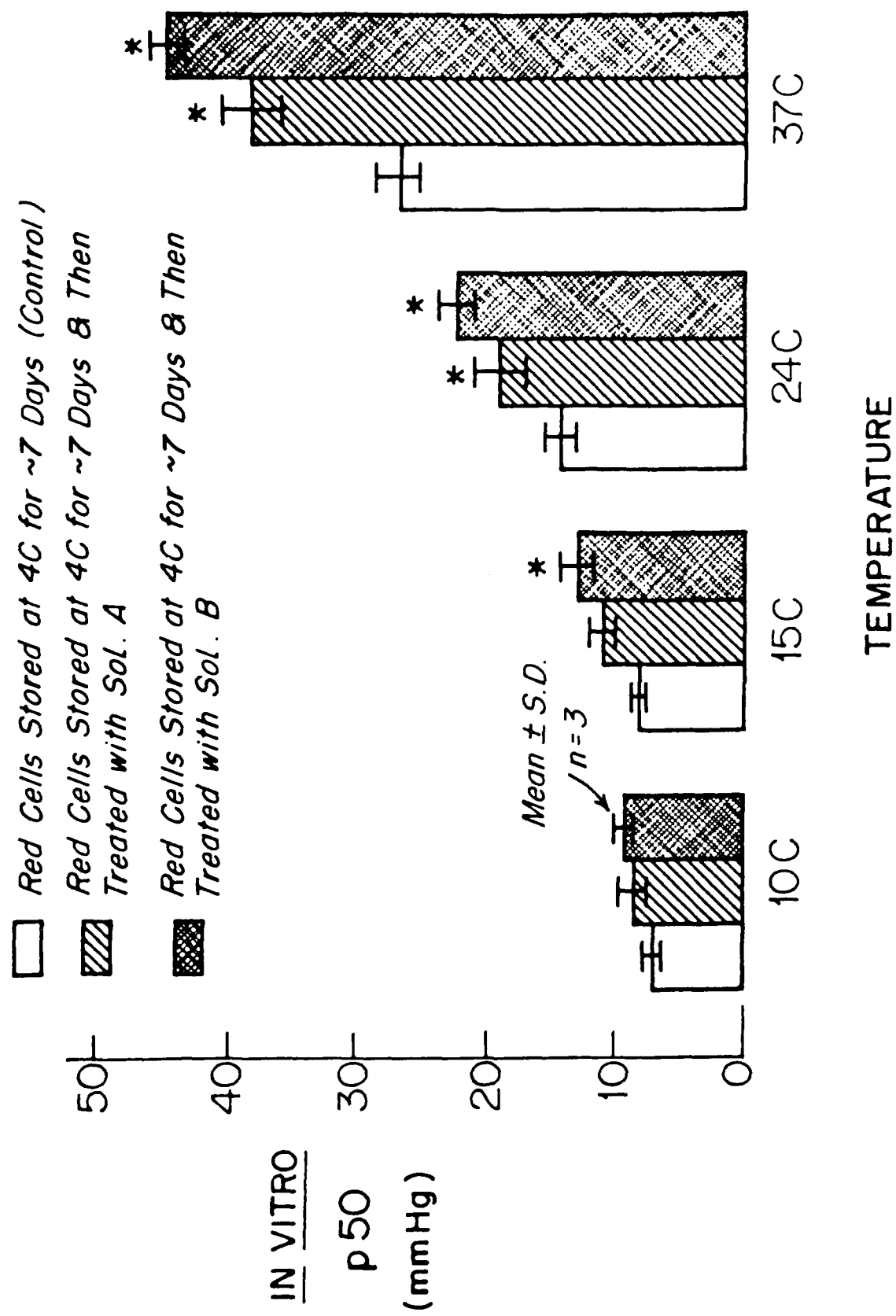
* $p < 0.05$ (Control vs. Sol. A or Sol. B)

Fig 15 -- The freeze-thaw-wash recovery, ^{51}Cr 24-hour posttransfusion survival, and index of therapeutic effectiveness (ITE) of red blood cells with 80% or 250% of normal 2,3 DPG after small aliquot (10 ml) autotransfusions with or without prior in vitro perfusion in a cardioplegic solution at 15 C. Aliquots from 5 units with 250% of normal 2,3 DPG were auto-transfused without prior perfusion. Three other units with 250% of normal 2,3 DPG were perfused in vitro for 3 hours, and an aliquot from each unit was labeled with ^{51}Cr and autotransfused. Two units with 80% of normal 2,3 DPG were perfused in vitro for 3 hours, and an aliquot from each unit was labeled with ^{51}Cr and autotransfused. (Reproduced with permission from Valeri CR, Crit Rev Clin Lab Sci, CRC Press, in press).

Not Pumped – Soln. C, Without Glucose

Pumped 3 Hrs. – Soln. C, With Glucose

Pumped 3 Hrs. – Not Rejuvenated

INDEX OF THERAPEUTIC EFFECTIVENESS

^{51}Cr 24 HR. POST-TX SURVIVAL (In Vivo)

RBC FREEZE-THAW-WASH RECOVERY (In Vitro)
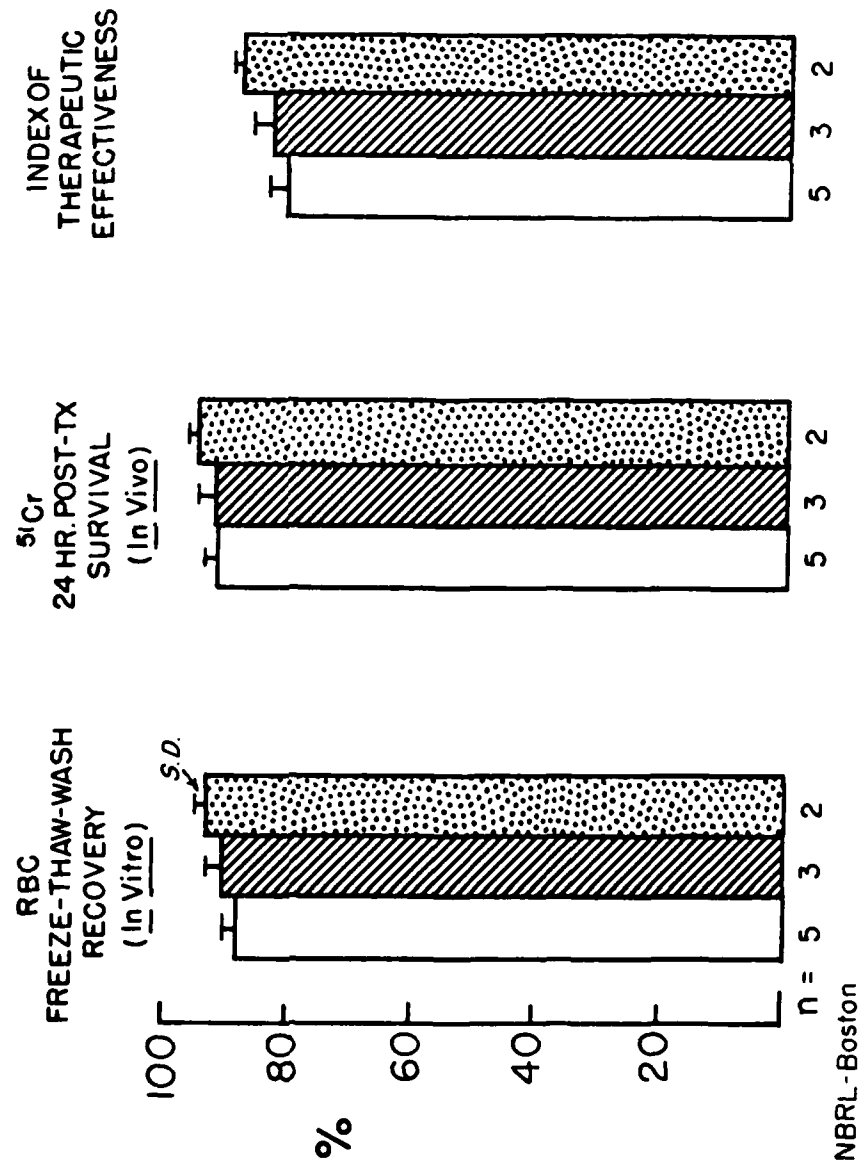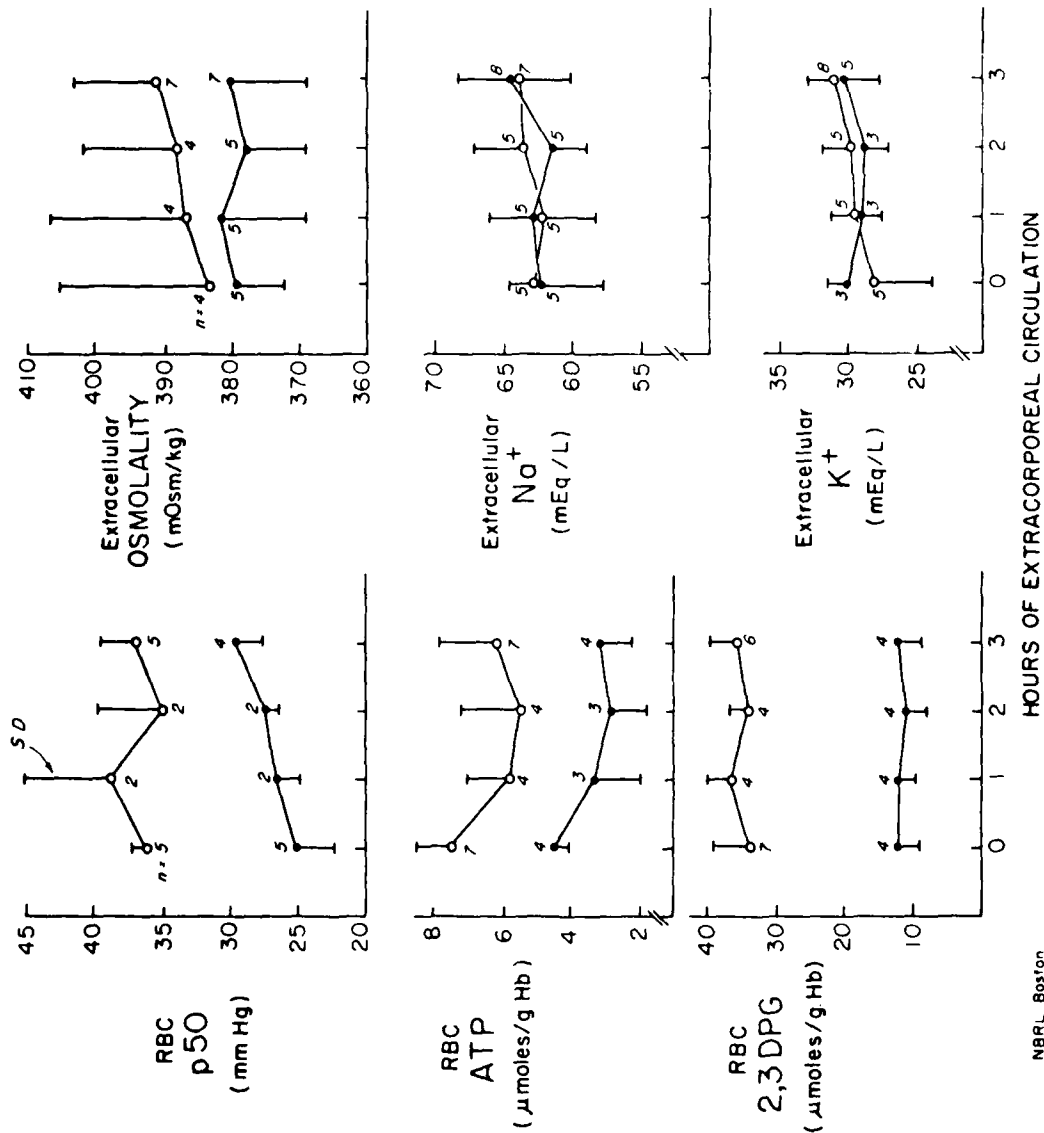
S.D.

%

100

80

60

40

20

n =

NBRL-Boston

Fig 16 -- Red blood cell 2,3 DPG, ATP, in vitro P_{50}, extracellular osmolality, and sodium ion and potassium ion of red blood cells with 80% of normal or 250% of normal 2,3 DPG perfused in vitro in a cardioplegic solution at 37 C, 22 C or 15 C. (Reproduced with permission from Valeri CR, Crit Rev Clin Lab Sci, CRC Press, in press).

● RBC with 80% of Normal 2,3 DPG
○ RBC " 250% " " "

Extracellular OSMOLALITY (mOsm/kg)

Extracellular Na⁺ (mEq/L)

Extracellular K⁺ (mEq/L)

RBC p50 (mm Hg)

RBC ATP (μmoles/g Hb)

RBC 2,3 DPG (μmoles/g Hb)

HOURS OF EXTRACORPOREAL CIRCULATION

NBRL, Boston

Fig 17 -- The supernatant hemoglobin of red blood cells with 80% of normal

2,3 DPG or 250% of normal 2,3 DPG perfused in vitro for 3 hours in a

cardioplegic solution at 37 C, 22 C and 15 C. (Reproduced with permission

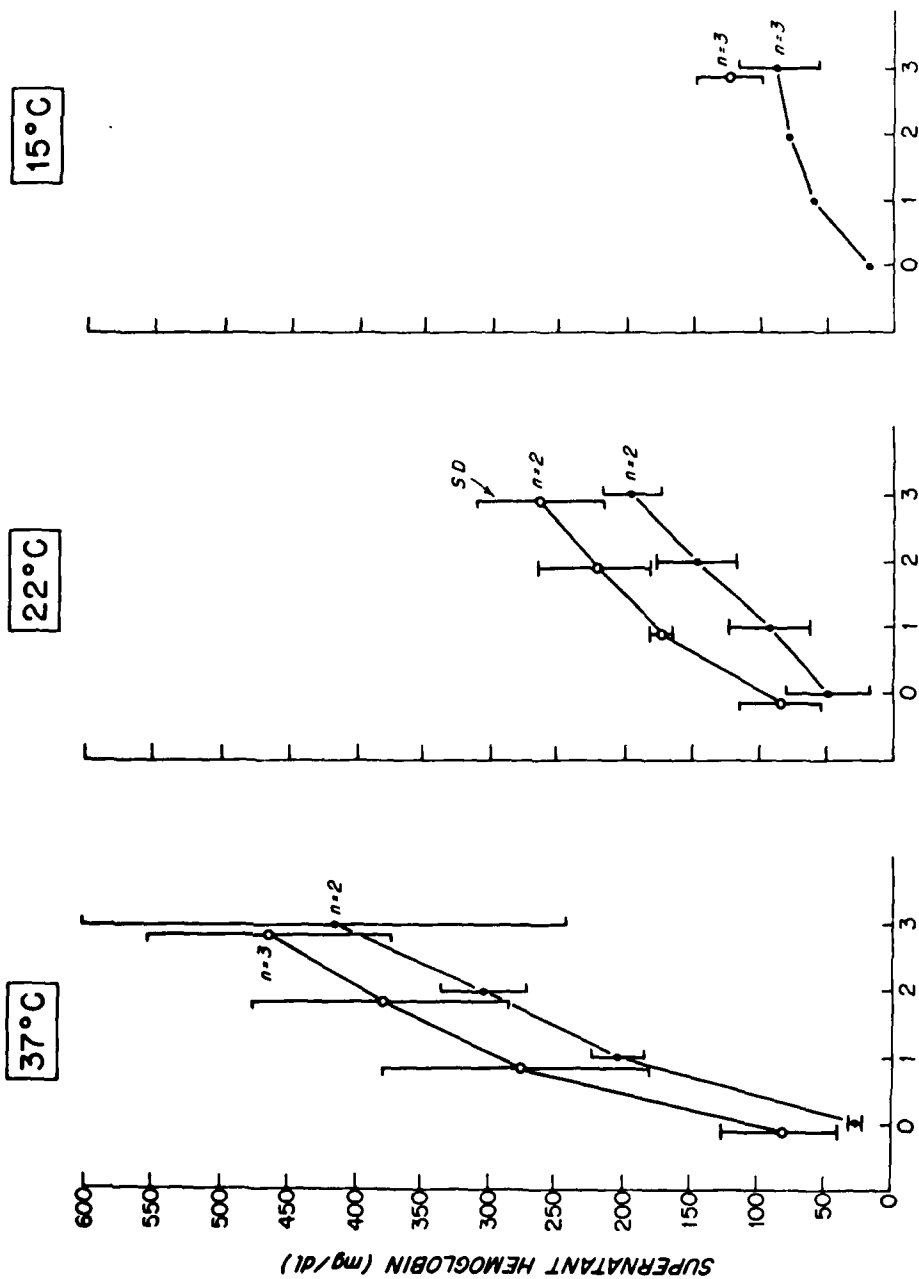from Valeri CR, Crit Rev Clin Lab Sci, CRC Press, in press).

- Non-rejuvenated Red Blood Cells
- Solution C Rejuvenated Red Blood Cells

15°C 22°C 37°C

SUPERNATANT HEMOGLOBIN (mg/dl)

HOURS OF EXTRACORPOREAL CIRCULATION

NBRL, Boston Ma , 1/80

Fig 18 -- The relation between PaO_2 and blood oxygen affinity at various levels of right to left shunt (S). The calculations were based on the following data. pH = 7.40, $PaCO_2$ = 40 torr, temperature 37 C, hemoglobin concentration = 15 gm/100 ml. The pulmonary arteriovenous difference of oxygen was 4 ml/100 ml. The oxygen tension at 50% saturation at normal acid-base state and temperature: newborn = 22, adult = 27, adult adapted to hypoxia = 32 and "Super-DPG" blood = 37 torr. (Reproduced with permission from Settergren G, Soderlund S, Eklop AC, Crit Care Med 1982;10:17).
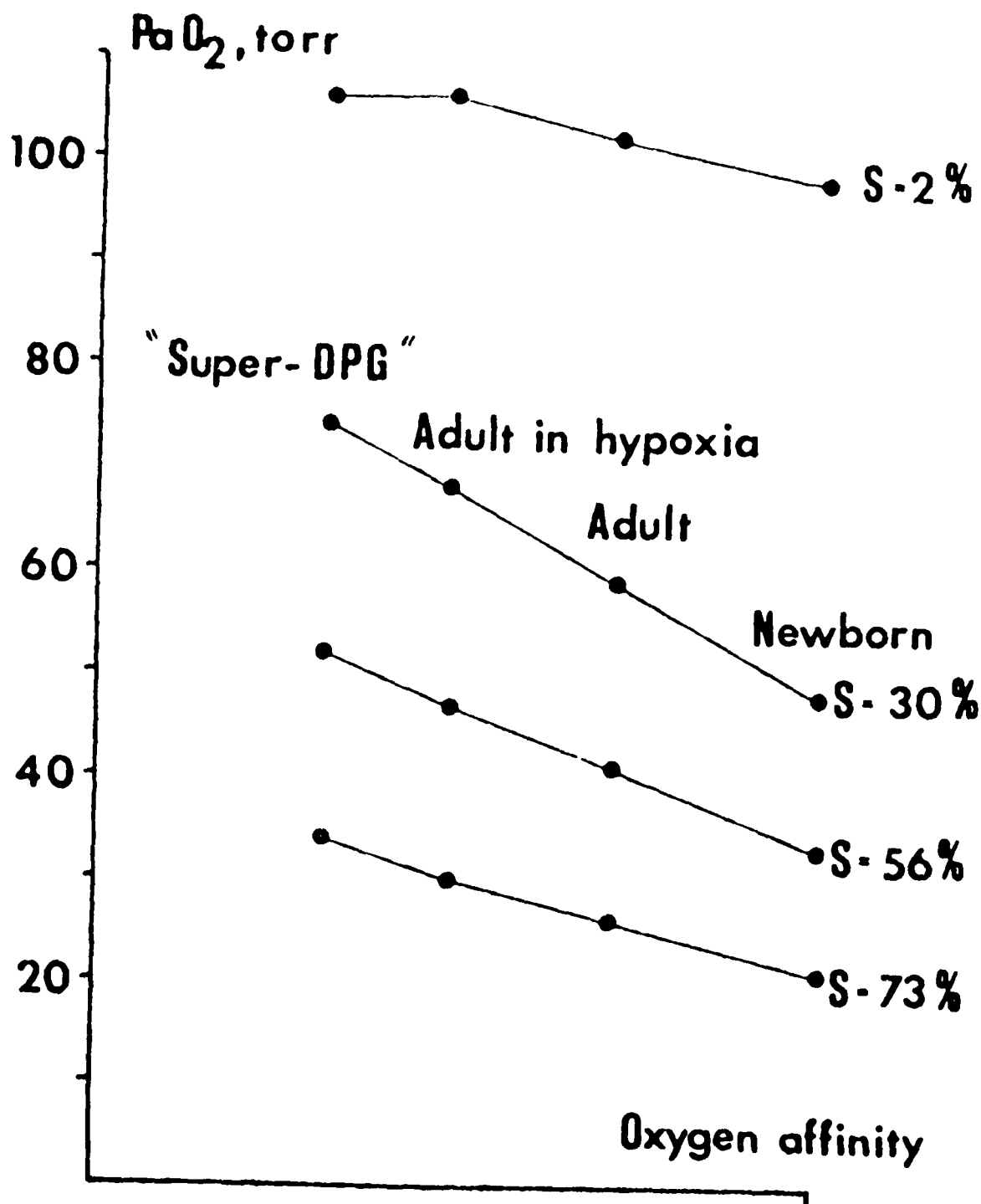
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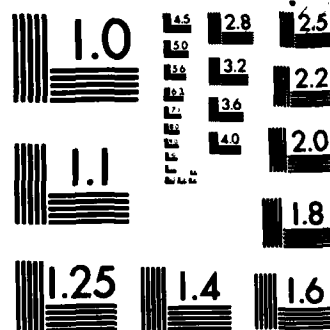
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